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Chester

MSc Nutrition and Dietetics

DNM001: Dissertation

A feasibility study of carbohydrate counting and
flexible insulin dosing in adults with type 2 diabetes:
**MATCH IT (MAatching Treatment to CarboHydrate in
Insulin-treated type Two diabetes)**

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Abstract

Background: Diabetes mellitus is a chronic condition which is associated with serious microvascular and macrovascular complications and diminished quality of life. Intensive glycaemic control has been shown to reduce the incidence of diabetes-related complications in people with type 2 diabetes mellitus (T2DM) but can further decrease quality of life. Carbohydrate counting and flexible insulin dosing is known to improve glycaemic control and quality of life in adults with type 1 diabetes (T1DM). Limited evidence suggests that this diabetes management method can also reduce glycosylated haemoglobin (HbA1c) in people with type 2 diabetes (T2DM) using prandial insulin (Bergenstal et al., 2008) but this has not been investigated rigorously and no studies have investigated the impact on psychosocial outcomes.

Research questions: Does insulin dose adjustment in line with mealtime carbohydrate intake in adults with T2DM using prandial insulin improve the primary outcomes HbA1c and quality of life? Impact on secondary outcomes including treatment satisfaction and vascular risk factors was also assessed.

Method: A feasibility study, using a randomised controlled delayed start (waiting list) trial design, was conducted. Adults with T2DM using prandial insulin were trained to count carbohydrates and adjust insulin doses through group education sessions.

Results: Carbohydrate counting and flexible insulin dosing in adults with T2DM was found to be non-inferior to static dosing insulin regimes, and was associated with improved quality of life and reduced perception of hypoglycaemia. This was associated with non-significant reductions in body weight, waist circumference and total daily insulin dose and was achieved despite increased dietary freedom, and without significant deterioration in other vascular risk factors.

Conclusions: This management method has the potential to improve quality of life whilst maintaining or optimising glycaemic control in individuals with T2DM who require a variable insulin regime. The rising incidence of T2DM, its economic and health burden, and the increasingly younger patient profile make these findings particularly pertinent. Further research is warranted to explore these initial findings.

Declaration of original work

I hereby declare that work contained herewith is original and is entirely my own work. It has not been previously submitted in support of a Degree, qualification or other course.

Signed.....Date.....

Presentation of work

Preliminary analysis of data contained in this report was presented at the Diabetes UK Professional Conference 2012 in Glasgow on 7th March 2013 as part of evidence in support of carbohydrate counting and flexible insulin dosing in type 2 diabetes in the debate "Carbohydrate Counting in Type 2 Diabetes: Effective or Not?"

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List of abbreviations

ADDQoL: Audit of Diabetes Dependant Quality of Life (questionnaire)

BMI: Body mass index

CP: Carbohydrate portion (10-12g carbohydrate)

CVD: Cardiovascular disease

DTSQ: Diabetes Treatment Satisfaction Questionnaire

DTSQc: Diabetes Treatment Satisfaction Questionnaire (change)

Group D: Delayed intervention group

Group I: Intervention group

HbA1c: Glycosylated haemoglobin

HDL cholesterol: High density lipoprotein cholesterol

IFCC: International Federation of Clinical Chemistry

MATCH IT: MAatching Treatment to **CarboH**ydrate in **Insulin**-treated type **T**wo diabetes

NHS: National Health Service

NICE: National Institute for Health and Clinical Excellence

QoL: Quality of life

T1DM: Type 1 diabetes

T2DM: Type 2 diabetes

TC: Total cholesterol

TDI: Total daily insulin dose

WBQ-12: Well-being questionnaire (12 questions)

WHO: World Health Organisation

1. Introduction

1.1 Impact of diabetes

Diabetes mellitus (diabetes) is a condition of abnormal blood glucose regulation, usually considered life-long, affecting approximately 2.9 million people in the UK (Diabetes UK, 2012). The most prevalent variant of diabetes, type 2 diabetes (T2DM) is strongly associated with obesity (De Fronzo, 2004) and occurs as a result of failing pancreatic β -cell function, responsible for the production of insulin, and insulin resistance. This is in contrast to Type 1 diabetes (T1DM), an auto-immune disease resulting in the destruction of pancreatic β -cells. Both conditions cause loss of the ability to maintain normoglycaemia through relative or absolute insulin deficiency.

Diabetes has significant implications for health and the economy in the UK. Hyperglycaemia, arising from inadequately controlled diabetes, is associated with the development of a number of pathologies including retinopathy, nephropathy, neuropathy and vascular disease. T2DM reduces life expectancy by up to 10 years, mainly due to increased cardiovascular disease (CVD) mortality (Roper, Bilous, Kelly, Unwin & Connolly, 2001). Diabetes is also associated with a reduction in quality of life (Holmes et al., 2000; Koopmanschap, 2002) and increased risk of depression (Jacobson, 1996). Diabetes results in huge costs to the National Health Service (NHS) in the UK; £23.7billion was spent on the condition in the 2010/2011 financial year, approximately 10% of total NHS expenditure, with around 80% of the direct costs of diabetes going to treat complications (Hex, Bartlett, Wright, Taylor & Varley, 2012). It is well established that the greater the frequency and degree of hyperglycaemia, determined by glycosylated haemoglobin (HbA1c), the higher the risk of diabetes complications for both T1DM and T2DM (Diabetes Control and Complications Trial [DCCT], 1993; DCCT/Epidemiology of Diabetes Interventions and Complications

[EDIC] Study Research Group, 2005; Turner et al., 1998). It is therefore a priority in diabetes management to achieve well-controlled blood glucose levels using drug therapy and lifestyle advice.

1.2 Management of type 2 diabetes

A large number of pharmacological therapies for the management of blood glucose levels in T2DM exist however the progressive nature of T2DM results in the eventual requirement of insulin treatment in many individuals. Carbohydrate counting and flexible insulin dosing as a diabetes management technique for T1DM has been shown to improve glycaemic control and quality of life (Dose Adjustment for Normal Eating [DAFNE] Study Group, 2002) and is advocated in the UK due to its clinical and cost-effectiveness (National Institute for Health and Clinical Effectiveness [NICE], 2003; NICE, 2004). This method of matching prandial insulin doses to blood glucose levels, predicted through assessment of mealtime carbohydrate intake, instead of adhering to static insulin doses, may aid glycaemic control in T2DM (Bergenstal et al., 2008) but its use is under-researched. Carbohydrate counting and flexible insulin dosing has the potential to improve clinical and patient outcomes in T2DM and its impact should be thoroughly assessed.

1.3 The research project

The following feasibility study was designed to assess the effect of educating adults with T2DM in carbohydrate counting and insulin dose adjustment techniques. This report explores the impact of diabetes in more detail, looks at current treatment options for T2DM and assesses the evidence for and against carbohydrate counting and flexible insulin dosing in this group. It describes the methodology and presents results of this study with reference to the effect on glycaemic control, psychosocial outcomes and vascular risk factors, discussing their relevance with regard to current literature.

2. Literature review

The following literature review investigates in more depth the basis for recommendations on glycaemic control in diabetes and the impact of diabetes on quality of life. It spans current treatment options in T2DM and discusses both the background to carbohydrate counting and insulin dose adjustment and its use in T2DM.

2.1 Glycaemic control in type 2 diabetes

2.1.1 Microvascular and macrovascular complications in diabetes

T1DM and T2DM are both associated with an increased risk of development of microvascular and macrovascular pathologies including cardiovascular disease (CVD), peripheral vascular disease, nephropathy, neuropathy and retinopathy (Skyler et al., 2009). Large landmark studies in the 1990s clearly showed for the first time that maintaining blood glucose levels close to the non-diabetic range prevented, delayed or slowed the progression of diabetes-related complications in both T1DM and T2DM (Diabetes Control and Complications Trial [DCCT], 1993; Turner et al., 1998). Both studies resulted in a change in clinical practice but were unable to show a reduction in macrovascular risk.

Evidence that good glycaemic control reduces the risk of the macrovascular complications myocardial infarction, stroke and death from CVD in T1DM came with the later study, a long term follow-up of the DCCT cohort, the Epidemiology of Diabetes Interventions and Complications (EDIC) study (DCCT/EDIC Study Research Group, 2005). Evidence from three large well designed studies in adults with T2DM since then has challenged the idea that macrovascular disease risk in T2DM is reduced with improved glycaemic control. The three studies, the Veterans Affairs Diabetes Trial

(VADT), Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study all showed no reduction in CVD events in intensive treatment groups compared to conventional treatment (ACCORD Study Group, 2008; ADVANCE Collaborative Group 2008; Duckworth et al., 2009). In contrast the STENO-2 study showed a 50% CVD risk reduction in T2DM with intensive therapy for glycaemic control, blood pressure, lipids and lifestyle (Gæde et al., 2003) although CVD risk reduction due to glycaemic control alone was not analysed. This is further complicated by the ACCORD study being prematurely terminated due to a higher mortality rate in the intensively treated group; however there was a trend towards lower incidence of cardiovascular events in some subgroups, leaving the possibility of benefit in intensive control on macrovascular disease risk in certain individuals with T2DM open.

The reason for the increased all-cause and cardiovascular mortality rate in the ACCORD study is unknown. Possible factors may have included the magnitude, or rate, of decrease of HbA1c, or the incidence of hypoglycaemia (Dluhy & McMahon, 2008). Hypoglycaemia has been linked to increased mortality by inducing cardiac arrhythmias and causing sudden death in both T1DM and T2DM (Heller, 2008; Lindström, Jorfeldt, Tegler & Arnqvist, 1992). As increased body mass index (BMI) and waist circumference are associated with increased CVD risk (Dobbelsteyn, Joffres, MacLean & Flowerdew, 2001; Wilson, D'Agostino, Sullivan, Parise & Kannel, 2002), decreases in cardiovascular risk in the ACCORD and VADT study may also have been negated by the weight gain occurring as a result of intensive control (Skyler et al., 2009). Whilst definitive evidence of the benefits of intensive glycaemic control on macrovascular outcomes in T2DM is lacking, the risk reduction of microvascular complications is well established. It is evident that treatments to optimise glycaemic

control in diabetes are vital but should not achieve this aim at the expense of weight gain or hypoglycaemia.

2.1.2 Glycaemic targets

Glycaemic targets for adults with T2DM should be personalised with reference to individual lifestyle and medical history but where possible, adherence to the national HbA1c target of 48mmol/mol should be promoted (NICE, 2009). In England in 2010-2011 only 26.4% of individuals with T2DM achieved HbA1c <48mmol/mol, and only 66.5% achieved HbA1c ≤58mmol/mol (Health and Social Care Information Centre, 2012) indicating considerable room for improvement. However the practice of monitoring targets in this way has been questioned as it does not allow for individualisation of glycaemic goals (Inzucchi et al., 2012). Achievement of glycaemic targets, individual or national, is challenging for many reasons and adults with T2DM may struggle with barriers to attaining their target including hypoglycaemia, prohibitive diet and lifestyle advice, side-effects of treatments and lack of knowledge and motivation.

2.2 Quality of life in diabetes

Quality of life (QoL) is a subjective perception of an individual's own physical, emotional and social well-being and is both difficult to define and difficult to measure. In recent years health-related quality of life (HRQoL), the quality of life determined by the presence and management of medical conditions, has become an increasingly important concept, considered by some to be our single most important clinical and research outcome (Polonsky, 2000) and the ultimate aim of all healthcare interventions (Rubin & Pevrot, 1999). Accordingly quality of life, not just length of life, is used to determine the cost-effectiveness of new treatments by NICE through the use of Quality-Adjusted Life Years (QALYs) (NICE, 2010).

QoL can be profoundly affected by T2DM in several ways. It is lower in individuals with T2DM compared to age-matched individuals without the disease (Holmes et al., 2000) and further declines with the onset of diabetes-related complications (Koopmanschap, 2002; Solli, Stavem & Kristiansen, 2010; Wexlar et al., 2006). It is unclear whether use of insulin in T2DM reduces QoL, with some research supporting (Koopmanschap, 2002) and other research refuting the idea (Pibernik-Okanoviæ, Szabo & Melko, 1998; Wandell, Brorsson & Åberg, 1998; Wexlar et al. 2006). It may be that insulin use acts as a proxy measure for disease progression and presence of diabetes complications, and when controlled for, the association with QoL diminishes (Wandell et al., 1998; Wexlar et al., 2006). Moreover use of insulin and improved glycaemic control can both result in greater frequency of hypoglycaemia (Wright et al., 1998), fear of which negatively impacts QoL in type 2 diabetes (Solli et al., 2010), although this has a small effect relative to the QoL decrement induced by diabetes-related complications (Matza et al., 2007). This is manifest in research showing a lower HbA1c does not improve QoL (Maddigan, Feeny, & Johnson, 2004; Wexlar et al., 2006) although this is not supported by all evidence (Lau, Qureshi, & Scott, 2004). The discordance in these results is perhaps attributable to the varying burden of hypoglycaemia within the two populations. This demonstrates that patients and clinicians can have the opposing goals of present quality of life versus optimal glycaemic control and future health; finding treatments that allow convergence of these goals is an unequivocal aim of research.

2.3 Pharmacological and lifestyle management of type 2 diabetes

T2DM is caused by the interaction of a number of genetic and environmental factors. It is estimated that approximately 80% of T2DM incidence is due to the metabolic

consequences of obesity (Gregg, Cheng, Narayan, Thompson, & Williamson, 2007). Consequently glycaemic control and risk of diabetes complications can be improved as a result of intentional weight loss in T2DM (Bosello, Armellini, Zamboni & Fitchet, 1997; Williamson et al., 2000). Furthermore remission of T2DM is a well-established result of bariatric surgery, although the mechanism appears not to be due to weight loss alone (Sala, Torrinhas, Heymsfield, & Waitzberg, 2012). It may also be possible to reverse T2DM through weight loss induced by severe dietary energy restriction without surgery (Lim et al., 2011). It is beyond the scope of this discussion to explore the literature on weight loss interventions in T2DM but it is recognised that a successful way to manage T2DM in many individuals would be weight loss (Nathan et al., 2009; NICE, 2009). Unfortunately with even the most efficacious multifactorial interventions, weight loss results are generally modest at best (NICE, 2006); bariatric surgery has a more profound effect on body weight and a predictable remission rate for T2DM (Buchwald et al., 2009) however is not suitable for many individuals. Pharmacological methods of managing T2DM will therefore be required until more effective methods of eliciting and maintaining weight loss are available, and for those individuals with significant pancreatic β -cell dysfunction.

There are a multitude of hypoglycaemic agents available for T2DM but as the disease progresses it becomes increasingly difficult to achieve good glycaemic control. Pancreatic β -cell function deteriorates at a rate of approximately 3-4% a year and many individuals with T2DM eventually require insulin replacement therapy (Wright et al., 1998). The optimal insulin regime for T2DM is not established and depends heavily on the individual's circumstances (NICE, 2009). Any insulin therapy will benefit an insulin-naïve adult with T2DM and poor glycaemic control (Holman et al., 2009) but if ill-matched to their lifestyle, and without sufficient education, insulin initiation can risk weight gain and hypo- or hyperglycaemia (Inzucchi, et al., 2012). Young adults can have significant variability in meal timing, frequency and content (Huang, Song,

Schemmel & Hoerr, 1994) therefore insulin management methods suited to dealing with this type of lifestyle are required to respond to the increasing prevalence of T2DM in younger age groups (Fox et al., 2006; Pinhas-Hamiel & Zeitler, 2005) and the serious mortality and morbidity resulting from poorly controlled diabetes. Basal-bolus insulin therapy, a combination of peak-less background insulin plus boluses of rapid-acting prandial doses, is closest to the physiological provision of insulin (Franc et al., 2009) and facilitates a higher degree of insulin adaptability. In addition, basal-bolus insulin therapy could be coupled with carbohydrate counting and insulin dose adjustment, described below, potentially providing the greater flexibility required.

2.4 Carbohydrate counting and insulin dose adjustment

Carbohydrate counting and insulin dose adjustment (or simply “carbohydrate counting”) employs knowledge of the macronutrient content of food to predict post-prandial blood glucose levels. It enables the user to calculate the most appropriate insulin dose for any meal, plus a corrective insulin dose for out-of-target blood glucose levels and accommodation of physical activity, instead of adhering to a static insulin dosing regime. Individuals on a basal-bolus insulin regime use this method of diabetes management by maintaining background insulin at a fairly static dose whilst quick-acting prandial insulin is titrated in accordance with glycaemia and carbohydrate intake, through use of insulin-to-carbohydrate ratios.

Carbohydrate counting allows the user to separate the decisions about healthy eating and insulin requirements, with the aim being good glycaemic control regardless of frequency and composition of meals (Heller et al., 2002). This is not currently an established management method for T2DM on basal-bolus insulin in the UK, meaning many individuals with T2DM either adhere to a rigid dosing regime, or alter their insulin doses based on experience, total quantity of food and/or blood glucose levels. Recent Diabetes UK guidelines for the management of T2DM concluded that the efficacy of

carbohydrate counting in insulin-treated T2DM is largely unknown (Dyson et al., 2011) reflecting a lack of research, rather than evidence of ineffectiveness.

The carbohydrate, protein and fat content of a meal, the glycaemic index of the carbohydrate, the time of day and a variety of other factors can affect post-prandial blood glucose levels, but carbohydrate load is the strongest predictor of the glycaemic response to a meal (Sheard et al., 2004). Carbohydrates cause 47-56% of the post-meal variation in glycaemia (Wolever & Bolognesi, 1996) and almost 100% of the carbohydrate within a meal is converted to glucose within 90 minutes (Laine, Thomas, Levitt & Bantle 1987). Within the majority of the physiological range there is a linear relationship between carbohydrate intake and insulin requirements (Halfon, Belkhadir & Slama, 1989) indicating post-meal insulin requirements can be estimated from the carbohydrate load of a meal. This led to the development of carbohydrate counting and insulin dose adjustment as a method of controlling blood glucose levels by mimicking endogenous insulin production in response to carbohydrate loads.

Algorithms advocating carbohydrate, protein and fat counting have been proposed to approximate insulin requirements (Howorka, Thoma, Grillmayr, & Kitzler, 1990), but only carbohydrate counting has been widely adopted and evidence suggests protein and fat counting algorithms are less effective (Franc et al., 2009). Carbohydrate counting and flexible insulin dosing is well established as an effective management method for T1DM (DAFNE Study Group, 2002; Laurenzi et al., 2011; Mehta, Quinn, Volkening, & Laffel, 2009; Mühlhauser et al., 1983) and has also been deemed cost-effective despite increased healthcare professional contact time during education (NICE, 2003). The seminal research investigating this technique in T1DM in the UK was the DAFNE (Dose Adjustment For Normal Eating) study. Educating participants in this method of diabetes management resulted in a drop in HbA1c of approximately 11mmol/mol, a reduction in severe hypoglycaemia and an improvement in quality of life

(DAFNE Study Group, 2002). Long term follow-up showed attrition in the improvement in HbA1c, yet quality of life remained significantly improved from baseline, even at four years post education (Speight et al., 2010).

2.5 Carbohydrate counting and insulin dose adjustment in type 2 diabetes

Although bearing similarities, T1DM and T2DM are diseases with very different aetiologies. The following discussion explores the suitability of carbohydrate counting and insulin dose adjustment in the context of T2DM physiology.

The pathogenesis of T2DM is complex and not fully understood. It appears to begin with a period during which endogenous insulin production is elevated to overcome hepatic insulin resistance (resulting in inappropriate gluconeogenesis and glycogenolysis and therefore elevated fasting plasma glucose) and reduced muscle insulin sensitivity (Taylor, 2008). Hyperinsulinaemia may result in normoglycaemia for a time until pancreatic β -cell function deteriorates, at which point overt diabetes can be identified. Pre-existing β -cell secretory dysfunction, identifiable in individuals with normal glucose tolerance and insulin sensitivity but genetically predisposed to T2DM, is also implicated in the development of T2DM (Alsahli & Gerich, 2010). Insulin production typically has an inverse relationship with time since diagnosis and the eventual decline of β -cell function necessitates insulin therapy initiation (DeFronzo, 2004).

An individual with T2DM remains biologically different to a person with T1DM despite a potentially identical therapeutic intervention. In T1DM endogenous insulin is minimal or absent (Atkinson & Eisenbarth, 2001) whilst in insulin-treated T2DM some insulin production ability is usually retained, albeit impaired (Taylor, 2008). This indicates that excursions from normoglycaemia may be greater in T1DM. In addition the

counterregulatory hormone response to hypoglycaemia which is lost in T1DM is at least partly preserved in T2DM offering a greater degree of protection against hypoglycaemia (Zammitt & Frier, 2005). Nevertheless a similarity between T1DM and T2DM is the inability to raise a post-prandial insulin response. Although there will be some endogenous insulin contribution in T2DM, it would be expected that individuals with T2DM would require higher insulin-to-carbohydrate ratios and have lower insulin sensitivity than T1DM as a result of the insulin resistance inherent in T2DM. Whether in a state of relative insulin deficiency, as in T2DM, or absolute insulin deficiency, as in T1DM, mealtime insulin requirements are determined by pre-prandial blood glucose levels plus post-prandial hyperglycaemia, the latter of which can be reliably predicted by carbohydrate counting.

It is surprising, considering the success of carbohydrate counting and flexible insulin dosing in T1DM and the physiological plausibility of using this method in T2DM, that there is a paucity of literature exploring the use of this technique in people with T2DM. This could be due to apprehension that the increased dietary freedom enabled by insulin dose adjustment would be detrimental to body weight and CVD risk factors, or that little would be gained in terms of glycaemic control due to the physiological differences outlined above. A small number of studies exist that suggest the potential success of carbohydrate counting in T2DM, and notably no studies indicate it is ineffective, although positive publishing bias cannot be discounted. A review of the current literature on carbohydrate counting in T2DM follows.

Good quality evidence for individuals with T2DM on basal-bolus insulin using carbohydrate counting and insulin dose adjustment amounts to one study. In a randomised controlled trial including 273 participants, Bergenstal et al. (2008) indicated that carbohydrate counting could be an effective method of glycaemic control in T2DM. They demonstrated no difference in HbA1c reduction between carbohydrate counting

and insulin dose adjustment, and using a simple algorithm method based on 3 day averages of blood glucose levels, to control glycaemia in a group of adults with T2DM. The average HbA1c in the carbohydrate counting group at the end of the 24 week study period was 48mmol/mol compared to 50mmol/mol in the algorithm group. The equality of success of the techniques is perhaps surprising presuming variability in mealtime carbohydrate intake in both groups and the authors acknowledge it is possible participants in the algorithm group had a more standardised carbohydrate intake, or that they adjusted their carbohydrate intake to suit their insulin doses, both of which would have resulted in an improved HbA1c in conjunction with the algorithm method. At the end of the study total daily insulin doses were significantly lower and there was a trend towards less weight gain in the carbohydrate counting group. Incidence of hypoglycaemia with blood glucose levels $<4.0\text{mmol/l}$ did not differ between groups but hypoglycaemia with blood glucose levels $<2.8\text{mmol/l}$ was more common in the carbohydrate counting group.

Further evidence includes Zipp, Roehr, Weiss and Filipetto's (2011) small scale pilot study of just six participants, four of whom completed the carbohydrate counting training. Results suggested an improvement in HbA1c with participants stating they felt an increased sense of ability to manage their diabetes (statistical analyses were not performed). Unfortunately this study involved too few participants to be able to deliver reliable conclusions and included participants on both insulin therapy and oral medication meaning the results are not transferable to a population of individuals on basal-bolus insulin therapy. It is also too disparate a group for a HbA1c change to represent a meaningful clinical improvement. In a slightly larger participant cohort, Rizvi (2005) showed a reduction in HbA1c from 72mmol/mol to 53mmol/mol for 17 patients with T2DM who were transferred from ineffective oral and/or insulin therapy to a basal-bolus insulin regime with education including carbohydrate counting. However this

study included no control group and improvements in glycaemic control may have derived from the change in pharmacological therapy alone.

More recently, when investigating efficacy of insulin pump therapy in T2DM, Leinung, Thompson, Luo, Leykina and Nardacci (2012) found that use of carbohydrate counting and prandial insulin calculator software was not superior to a static dose regime. This retrospective study only included a small number of participants and all individuals were taught to carbohydrate count prior to receiving a pump therefore, even if this management technique was not actively used, all participants were carbohydrate-aware. Due to lack of randomisation, the participants in the carbohydrate counting group had a higher mean baseline HbA1c, and a slightly higher HbA1c at 6 months meaning glycaemic control results were difficult to interpret. Furthermore, the distinction between individuals who were carbohydrate counting and those using static doses was based on the most frequent bolus dosing method, static or adjusted, and there may have been considerable overlap of use of methods between groups. It cannot be concluded with certainty whether carbohydrate counting was beneficial in adults with T2DM on insulin pumps.

In conclusion, carbohydrate counting and insulin dose adjustment in T2DM is an under-researched area, particularly with regard to its impact on psychosocial outcomes which have not been examined at all. With its success in T1DM, carbohydrate counting and insulin dose adjustment is a good candidate to explore for the management of T2DM.

2.6 Summary of literature

Adults with T2DM are vulnerable to increased mortality and morbidity, and diminished health-related quality of life arising from their condition. Treatments to improve glycaemic control can result in further decrements in QoL. Despite many developments in diabetes care, there is still certainly potential to offer treatments that more effectively enable achievement of individual glycaemic targets whilst minimising impact on QoL. Given the proven effectiveness of carbohydrate counting and flexible insulin dosing in T1DM, both in improving glycaemic control and QoL, and the potential value of offering individuals with T2DM on basal-bolus insulin greater flexibility than conventional treatments, studies to investigate its impact on HbA1c and QoL are clearly warranted. This feasibility study will explore the effect of insulin dose adjustment in line with mealtime carbohydrate intake on biomedical and psychosocial parameters in adults with T2DM and could inform further research with the potential to enhance the future management of adults with T2DM.

2.7 The research questions

2.7.1 Aim of project

The aim of the research was to evaluate the impact of training in carbohydrate counting and insulin dose adjustment on biomedical and psychosocial outcomes in adults with T2DM on a basal-bolus insulin regime.

2.7.2 Primary research question

Does carbohydrate counting and flexible insulin dosing affect HbA1c or QoL in adults with T2DM on a basal-bolus insulin regime?

Primary outcomes: HbA1c and QoL questionnaire

Null hypotheses:

- Carbohydrate counting and flexible insulin dosing does not affect HbA1c
- Carbohydrate counting and flexible insulin dosing does not affect QoL

2.7.3 Secondary research question

Does carbohydrate counting and flexible insulin dosing affect proportion of patients achieving HbA1c <53mmol/mol, incidence of hypoglycaemia, total daily insulin doses (TDI), general well-being, treatment satisfaction or vascular disease risk factors in adults with T2DM on a basal-bolus insulin regime?

Secondary outcomes: Self-reported incidence of hypoglycaemia and TDI, general well-being and treatment satisfaction questionnaires, BMI, waist circumference, blood pressure and lipid profile

3. Methods

3.1 Study design

This original quantitative research was a yearlong feasibility study examining the impact of the educational intervention **MATCH IT** (**MA**atching **T**reatment to **CarboH**ydrate in **I**nsulin-treated type **T**wo diabetes) designed to teach carbohydrate counting and insulin dose adjustment to adults with T2DM on basal-bolus insulin. A pilot randomised delayed start (waiting list) trial design was used to investigate the dependent variables glycaemic control, quality of life and vascular risk factors, whilst manipulating the independent variable carbohydrate counting and insulin dose adjustment training and observing confounding factors physical activity levels and alcohol intake. Participants were randomly split into 2 groups, one group receiving the educational intervention at baseline, the immediate intervention group (Group I), and the other receiving it 6 months after baseline, the delayed intervention group (Group D). For the first six months participants allocated to the delayed intervention group acted as a control group by continuing to receive standard care, which included any appointments with clinicians already planned, and continuing with usual insulin doses and dose adjustments. The design was based on a study involving flexible insulin management in people with type 1 diabetes (DAFNE Study Group, 2002).

3.1.1 Ethical approval

This study was granted ethical approval from the North West 1 Research Ethics Committee (Cheshire) on 12th November 2010 (Appendix 1) and was accepted by the Countess of Chester Hospital NHS Foundation Trust Research and Development Department. Sponsorship was provided jointly by the University of Chester and the Countess of Chester Hospital NHS Foundation Trust (Appendix 2).

Ethical approval was also granted for analyses of data regarding insulin-to-carbohydrate ratios and adiposity but this was later acknowledged to be beyond the scope of this thesis.

3.1.2 *Dependent variables*

3.1.2.1 *HbA1c and lipid profile*

Non-fasting blood samples were obtained by phlebotomy staff at the Countess of Chester Hospital and analysed in the on-site laboratory to provide HbA1c and lipid profile data including total cholesterol (TC), high density lipoprotein (HDL) cholesterol and triglycerides. HbA1c was reported in IFCC (International Federation of Clinical Chemistry) units.

3.1.2.2 *Anthropometry*

Height was measured using a Seca stadiometer; measurements were recorded to the nearest 0.1cm. Weight was measured using Seca scales (calibrated annually) and recorded to the nearest 0.1kg. Waist circumference was measured to the nearest 0.5cm in accordance with international guidelines (World Health Organisation [WHO], 2011) using a tape measure placed midway between the lowest palpable rib and the top of the iliac crest.

3.1.2.3 *Blood pressure*

Systolic and diastolic blood pressure was measured using a Welch Allyn digital sphygmomanometer (calibrated annually).

3.1.2.4 Insulin doses, hypoglycaemia, medical & drug history and lifestyle

A researcher-administered questionnaire (Appendix 3) was used to collect insulin dose and hypoglycaemia information. Total daily insulin doses (TDI) were collected as patient-reported average doses. Incidence and severity of hypoglycaemia was recorded as patient-reported average number of hypoglycaemic episodes per month; severity classification was based on American Diabetes Association Workgroup on Hypoglycaemia (2005) definitions for hypoglycaemia. Medical and drug history and lifestyle information was gathered to monitor as confounding factors and for eligibility. Physical activity level was measured subjectively using patient-reported grade of sedentary, light, moderate, or intensive with a standardised definition given by researcher. Alcohol intake was recorded as patient-reported average units per week.

3.1.2.5 Questionnaires

The Audit of Diabetes Dependent Quality of Life (ADDQoL) questionnaire, Diabetes Treatment Satisfaction Questionnaire (DTSQ), Diabetes Treatment Satisfaction Questionnaire - change (DTSQc) and Well-Being Questionnaire (W-BQ12) (Appendix 4) were obtained from Health Psychology Research Ltd with an approved licence application (Appendix 5).

The ADDQoL questionnaire was used three times throughout the study - at baseline, six and twelve months. This questionnaire was developed for use specifically in diabetes (Bradley et al., 1999) and has subsequently been improved, the most up-to-date version being used as part of this research (Wee, Tan, Goh & Li, 2006). It is designed to capture the effect of diabetes on nineteen different aspects of quality of life, including dietary freedom, and allows weighting of scores according to importance for the subject. For example a participant might report that diabetes has a large

negative effect on their financial circumstances but if finances are not important to them then this will provide a low weighted score. Combining all weighted scores generates an average weighted impact (AWI) score indicative of overall effect of diabetes on all aspects of quality of life considered. In addition it provides two overview question scores on general present quality of life and quality of life as affected by diabetes.

The DTSQ questionnaire (Bradley, 1994) assesses current satisfaction with treatment through six questions and the DTSQ (change) questionnaire (Bradley et al., 2000) determines how participants' satisfaction with their treatment is different compared to their previous treatment. In addition both assess perceived frequency of hypoglycaemia and hyperglycaemia. The DTSQ was used three times throughout the study, at baseline, six and twelve months, whilst the DTSQc was used only once, 6 months after the educational intervention (at 6 months for the intervention group and at 12 months for the delayed intervention group) to compare satisfaction with the management method taught by MATCH IT to their previous static insulin dose regime. A revision to the text of the two questionnaires was employed to clarify their use with regard to the current study.

The W-BQ12 is designed to assess twelve aspects of positive and negative well-being which are combined to provide a general well-being score (Bradley and Lewis, 1990; Riazi et al., 2006) and was used at baseline, six and twelve months. Together with the DTSQ, these questionnaires have been advocated by the World Health Organisation (WHO) and International Diabetes Federation (IDF) as tools to monitor psychological outcomes in diabetes care (Bradley & Gamsu, 1994).

All three questionnaires have been validated in adults with diabetes (Wee, Tan, Goh & Li, 2006; Pouwer, Snoek, & Heine, 1998; Pouwer, van der Ploeg, Adèr, Heine & Snoek, 1999) and have proven sensitive to changing from a rigid to a flexible insulin regime (DAFNE Study Group, 2002). Scoring of the questionnaires and treatment of missing

data followed questionnaire guidance (Bradley, 2010a; Bradley 2010b; Bradley 2010c; Bradley 2010c).

3.2 Population and subjects

3.2.1 Sample and sample size estimation

Data did not exist to allow a meaningful sample size calculation for this feasibility study but a sample size was estimated using G*Power software version 3.1.2 (Buchner, Erdfelder, Faul & Lang, 2009).

Based on results from the DAFNE study, the effect size of the intervention was $d=0.79$ for a 10mmol/mol drop in HbA1c and $d=0.86$ for a 63% improvement in the ADDQoL question regarding dietary freedom in the DAFNE arm. To detect a 10mmol/mol drop in HbA1c in the intervention group with 80% power ($p<0.05$, two-tailed), 27 participants in each arm were required. To detect a 63% improvement in sense of dietary freedom in the intervention group with 80% power ($p<0.05$, two-tailed), 23 participants in each arm were required.

As this study has more than one primary outcome, as is common in modern clinical trials, the sample size should be sufficient to detect differences in both the outcomes hence a sample size of at least 27 participants in each arm would be required. It is possible that effect size of this intervention would be smaller in a sample of adults with T2DM, meaning the required sample size is here underestimated. However the size of the sample for this feasibility study had to be pragmatically based on the minimum number of participants to make the study design viable, which was estimated at 8 in each arm, and the maximum number that would be manageable given the constraints of the time and resources of a Masters project and the limited eligible population in the Cheshire area, estimated at 15 participants in each arm.

3.2.2 Population and recruitment

Suitable potential participants, adults with T2DM on basal bolus insulin from the Countess of Chester Hospital NHS Foundation Trust Diabetes Unit, were identified by a computerised search of Countess of Chester Hospital electronic medical records. This was carried out using relevant search terms including type 2 diabetes and prandial insulin brand names. The records searched were those created by diabetes doctors during annual review appointments at the Diabetes Centre. Potential participants' electronic medical records were then manually checked for eligibility. In addition the diabetes team were informed of the eligibility criteria for the study and opportunistically recruited participants from clinic appointments. Potential participants were invited into the study by letter (Appendix 6) and telephone calls.

3.2.3 Eligibility criteria

3.2.3.1 Inclusion criteria

- Male or female aged 18 years+ with type 2 diabetes
- Self-administering prandial insulin at least twice daily, with or without long-acting insulin, for at least 6 months.
- If taking metformin, stable dose for 3 months prior to study.
- Willingness to learn carbohydrate counting and flexible insulin dosing management methods and adhere to study procedures.
- Deemed medically suitable to participate by consultant diabetologist at Countess of Chester Hospital

3.2.3.2 *Exclusion criteria*

- Acute illness.
- Inability to communicate in spoken and written English.
- Pregnancy.
- Lack of awareness of hypoglycaemia.
- Use of anti-diabetic medication except metformin.

3.2.4 *Consent*

The research was discussed with potential participants over the telephone and in person, and a Participant Information Sheet (Appendix 7) was provided at least one week prior to the first appointment. Written informed consent was gained using the study Consent Form (Appendix 8) at the first appointment, prior to commencing any study procedures.

3.2.5 *Participant reimbursement*

Participants received reimbursement for travel expenses and parking costs incurred as a result of complying with study procedures which was funded through grant monies awarded by Sanofi-Aventis for this project.

3.3 Procedures

All study procedures were carried out by the author of this thesis who is a registered dietitian. In line with specialist diabetes service provision recommendations (Goenka, Turner & Vora, 2011), local agreements are in place at the Countess of Chester Hospital NHS Foundation Trust permitting competent Diabetes Specialist Dietitians to support and advise patients on insulin dose adjustment.

3.3.1 Randomisation

Participants and the researcher were not blinded to treatment allocation. Participants were randomised into either Group I or Group D using a permuted block method with a random number sequence generated by Random.org (Haahr & Haahr, 1998) to ensure equal numbers of participants in each group. Group allocations were written down and placed in opaque envelopes by a member of staff not involved in the research. At the end of each initial data collection appointment, after consent was obtained, the envelopes were opened in order and participants informed of their group assignment.

3.3.2 Study procedure

All study visits took place in the Countess of Chester Hospital Diabetes Unit. Figure 1 outlines study procedures. Group I commenced MATCH IT less than 2 weeks after the baseline data collection visit and Group D commenced MATCH IT less than 2 weeks after the six month data collection visit.

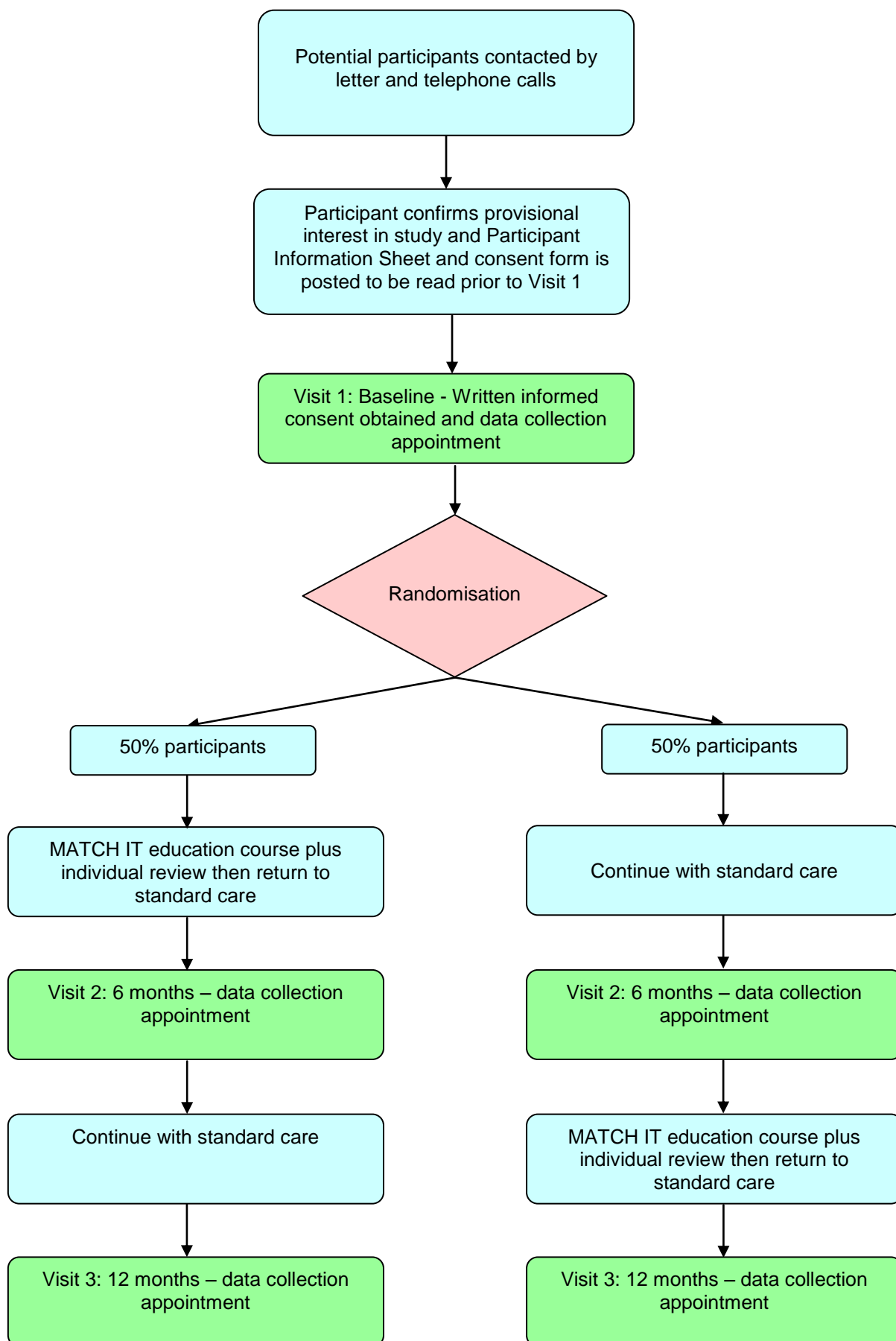


Figure 1 Flowchart indicating study procedures

3.3.3 MATCH IT

The educational intervention **MATCH IT** (**MA**atching **T**reatment to **CarboH**ydrate in **I**nsulin-treated type **T**wo diabetes) comprised two half-day group education sessions on two consecutive weeks at the Countess of Chester Hospital, followed by an individual review appointment. If additional support was required after the MATCH IT course, this was provided as part of the routine care offered by the team at the Diabetes Centre in the hospital.

The MATCH IT course content and resources were developed specifically for the study and were based on an existing successful carbohydrate counting and insulin dose adjustment course for T1DM at the Countess of Chester Hospital (Patel et al., 2010) and Diabetes UK workbooks (Diabetes UK, 2008). MATCH IT was delivered by a Diabetes Specialist Dietitian, the author of this thesis, with a focus on improving glycaemic control and facilitating dietary flexibility through carbohydrate counting and insulin dose adjustment. Glycaemic targets of 4.0-7.0 mmol/l pre-meal and 2 hours post-prandial <8.5mmol/l were recommended as per national guidance (NICE, 2009). Personalised insulin-to-carbohydrate portion (insulin:CP) ratios and correction factors were calculated directly from participants' blood glucose and food diaries (calculations provided in Appendix 9). Four MATCH IT courses ran in total, two for each arm, with five participants in each. The MATCH IT education sessions were standardised by using a defined lesson plan and presentation ensuring consistent reproducibility. The course content is outlined in Figure 2; a course manual was provided to support learning. Participants' GPs were informed by letter of their contribution to the research (Appendix 10).

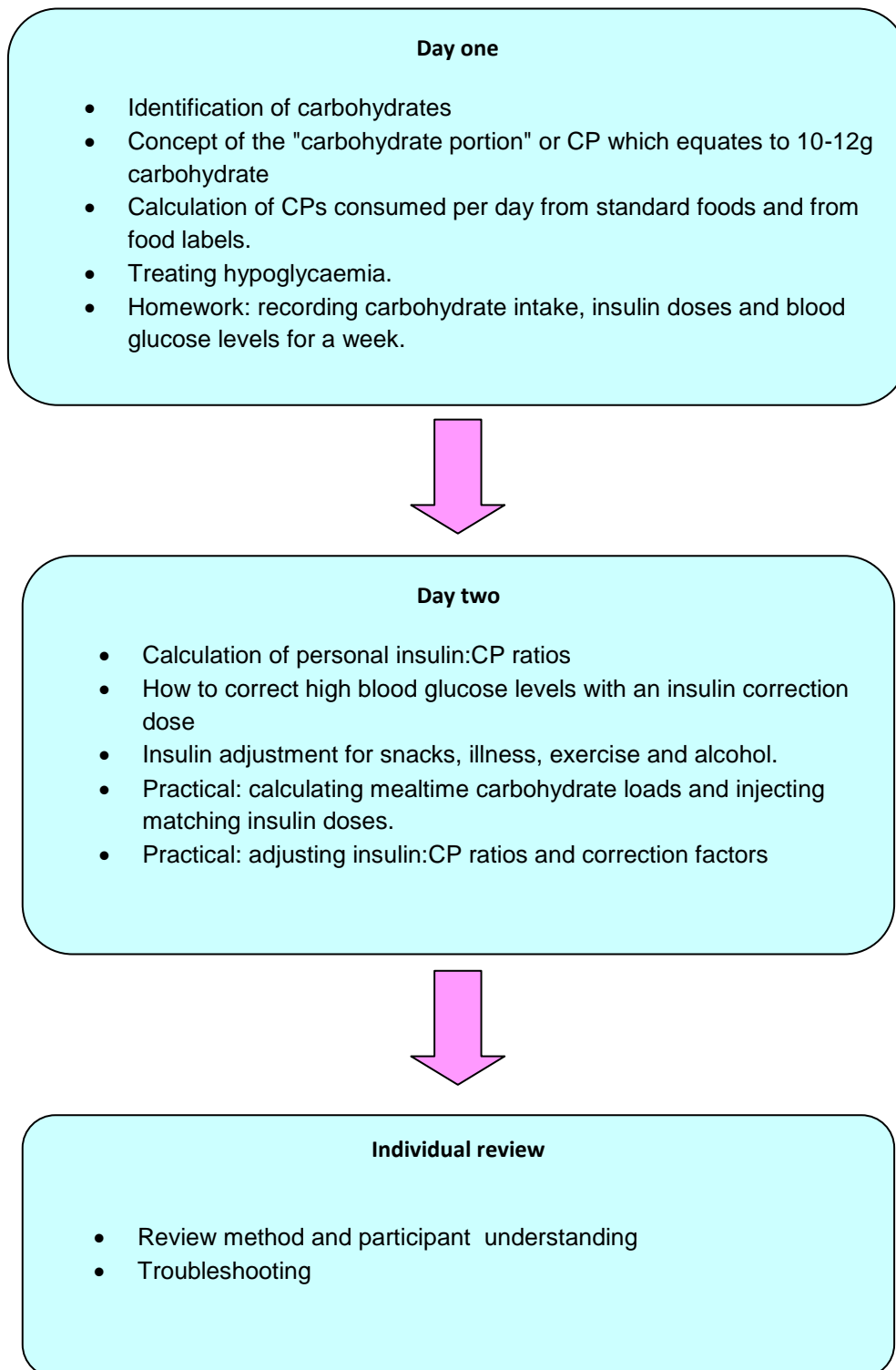


Figure 2 MATCH IT programme content

3.4 Statistical analyses

Data was analysed using the statistical package SPSS Statistics 19 (IBM). For all tests an α -level of 0.05 (two-tailed) was considered statistically significant and confidence intervals of 95% were used to interpret findings; exact significances were calculated because the sample size was small.

Descriptive statistics were used to explore the data initially followed by the use of appropriate graphs and inferential statistics to highlight trends or differences. Preliminary analyses, namely Shapiro-Wilk tests, indicated that some variables followed the distribution of a normal Gaussian curve. The Shapiro-Wilk test is appropriate for $3 < n < 5000$ (Royston, 1995), but, although it performs better than other tests for normality when using small sample sizes, it has low power to detect deviations from a normal distribution in a very small sample size such as $n < 10$ (Razali & Wah, 2011), as was the case in the present research. It was therefore interpreted in conjunction with histograms, Q-Q plots and detrended Q-Q plots.

Visual inspection of the data was challenging due to the small sample size but showed skewed data and the presence of outliers in several variables, for example HbA1c, TDI, and BMI, despite normality tests signifying no significant difference from a normal distribution. Examples of such normality test results and histograms, Q-Q plots and detrended Q-Q plots are provided in Appendix 11. Log, square root and reciprocal transformations were unsuccessful at creating normally distributed data in those that were not normally distributed. Non-parametric tests were therefore used when comparing actual values, as these are robust to deviations from the normal distribution.

Medians and interquartile ranges were calculated as these measures of central tendency and spread are less sensitive to the presence of outliers. Chi-squared was used to examine the number of participants allocated to each group. Fisher's exact test

was used to investigate the relationship between group allocation and drop-out, number of females in each group, and physical activity, as an expected frequency of $n < 5$ occurred in some groups.

It was not possible to calculate percentage change in variables over time for all variables as QoL data included scores of zero from which it is not possible to calculate percentage change. Mann Whitney U tests were therefore used to explore actual change in biomedical and psychosocial variables from baseline to 6 months as a result of group allocation, and relationship of HbA1c to participant drop-out. Wilcoxon signed-rank tests for related samples compared the distribution of medians of sequential baseline and six month biomedical and psychosocial variables within each group. In Group I only a Friedman ANOVA test was used to detect differences in sequential biomedical and psychosocial data from baseline, six and twelve months. Data was analysed per-protocol except for attrition rate.

In Group D only 2 participants provided data at twelve months severely limiting statistical analysis. Discussion and analysis of the data was inappropriate as the sample may be misrepresentative of the participant group as a whole. Twelve month data for these two participants are therefore provided as means (median and interquartile range not possible) but excluded from analyses and graphs.

4. Results

4.1 Participant flow

Seventy-nine potential participants were contacted regarding the MATCH IT study. Of the forty-one participants identified as eligible, nineteen were randomised representing a 46% uptake of the research project. Figure 3 illustrates participant flow through the study. Only nine participants provided data at all three time points resulting in a 53% attrition rate overall. By 12 months significantly more participants had left the study in the delayed intervention arm (8 out of 10 participants) than in the immediate intervention arm (2 out of 9 participants) ($p=0.023$). Of those participants from both groups that withdrew from the study, 4 (40%) dropped out during or after the MATCH IT course compared to 6 participants (60%) who dropped out prior to receiving any carbohydrate counting and flexible insulin dosing training. HbA1c at baseline did not differ between study completers and non-completers ($n=19$, $U=36.5$, $p=0.497$). Not all individuals who completed MATCH IT used the technique consistently but adherence to carbohydrate counting and insulin dose adjustment principles were not measured.

4.2 Baseline characteristics

Overall the group consisted of older, obese adults with poorly controlled T2DM (**Error! Not a valid bookmark self-reference.**). All participants were Caucasian and all took both basal and bolus insulin. 47% (8 participants) were on insulin glargine, 47% (8 participants) were on insulin detemir and 6% (1 participant) used isophane insulin as a long-acting insulin. 88% (15 participants) used insulin aspart as a prandial insulin whilst 6% (1 participant) used insulin glulisine and 6% (1 participant) used insulin lispro. No participant had ever experienced severe hypoglycaemia.

At baseline Group I and Group D were similar with no statistical differences in demographic or biomedical characteristics between the groups (**Error! Not a valid bookmark self-reference.**) or in quality of life (QOL), treatment satisfaction scores or perceived hyperglycaemia (Table 2). However participants in Group I perceived they had a significantly higher number of episodes of hypoglycaemia compared to Group D at baseline.

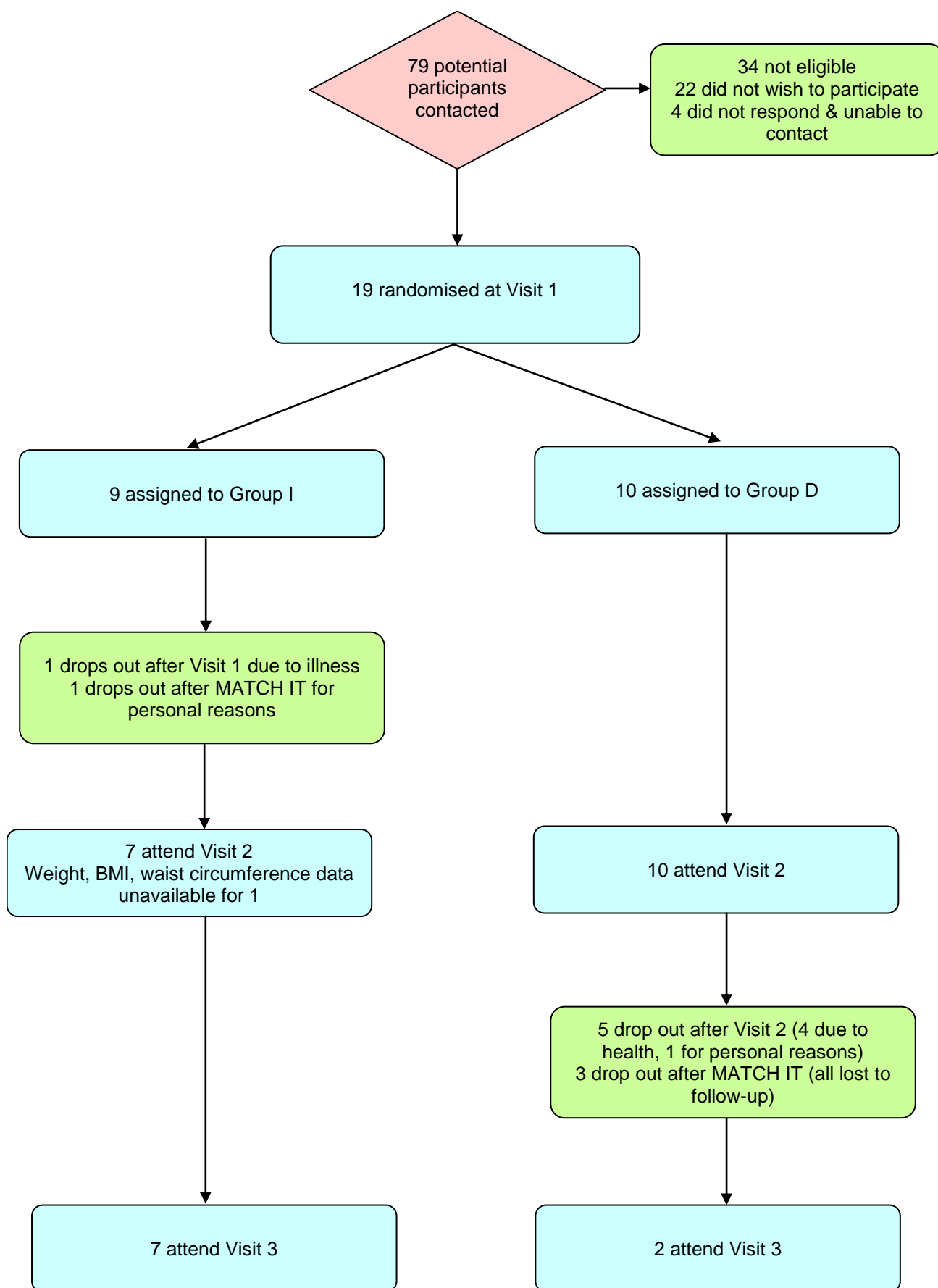


Figure 3 Consort flowchart indicating participant flow through study

Table 1 Comparison of baseline demographic and biomedical characteristics between groups. Values are median (interquartile range) unless otherwise stated.

Variable	Group I n=7	Group D n=10	Statistical values
Number of patients (% in parentheses)	7 (41)	10 (59)	$\chi^2(1)=0.529$ p=0.629
Number of females (% in parentheses)	3 (43)	3 (30)	p=0.644
Age (years)	66 (55-69)	61 (53-70)	U=31.0 p=0.740
Duration of diabetes (years)	17.0 (15.0-28.0)	11.0 (7.5-28.5)	U=18.5 p=0.109
HbA1c (mmol/mol)	58 (45-66)	74 (47-81)	U=48.5 p=0.193
Total daily insulin dose (units)	84 (42-116)	71 (48-143)	U=33.0 p=0.887
Episodes of hypoglycaemia per month	1.0 (1.0-3.0)	0.5 (0.0-4.7)	U=25.0 p=0.364
Weight (kg)	93.6 (85.5-105.0)	99.9 (93.4-111.1)	U=47.0 p=0.270
BMI (kg/m ²)	31.6 (27.1-34.3)	33.3 (31.9-35.5)	U=46.0 p=0.315
Waist circumference (cm)	118.0 (111.0-121.0)	118.5 (113.3-127.0)	U=37.5 p=0.813
Systolic blood pressure (mmHg)	133 (100-156)	133 (123-152)	U=35.5 p=1.000
Diastolic blood pressure (mmHg)	70 (60-79)	76 (67-87)	U=44.5 p=0.364
Total cholesterol (mmol/l)	3.0 (2.7-4.0)	3.9 (3.6-4.6)	U=51.5 p=0.109
HDL cholesterol (mmol/l)	1.0 (0.8-1.2)	1.1 (0.8-1.2)	U=34.0 p=0.962
Triglycerides (mmol/l)	1.4 (1.2-2.8)	2.3 (1.3-2.9)	U=38.5 p=0.740

Table 2 Comparison of baseline QoL and treatment satisfaction scores between groups. Values are median (interquartile range).

Variable	Group I n=7	Group D n=10	Statistical values
Present quality of life □	1.0 (0-1.0)	1.0 (0-2.0)	U=40.5 p=0.601
Impact of diabetes on quality of life ¥	-2.0 (-2.0 - -1.0)	-2.0 (-2.3 - -1.0)	U=36.0 p=1.000
Average weighted impact of diabetes on quality of life ◆	-2.8 (-4.5 - -0.8)	-3.7 (-4.3 – 0)	U=38.0 p=0.813
Weighted impact of diabetes on “freedom to eat as I wish” ◆	-4.0 (-6.0 - -1.0)	-4.0 (-7.5 – 0)	U=33.0 p=0.918
Weighted impact of diabetes on “freedom to drink as I wish” ◆	-2.0 (-4.0 – 0)	-4.0 (-6.0 – 0)	U=27.5 p=0.681
Overall treatment satisfaction †	28.0 (22.0-36.0)	25.0 (23.0-29.0)	U=22.5 p=0.536
Perceived hyperglycaemia •	2.0 (2.0-5.0)	2.0 (0-4.0)	U=19.5 p=0.336
Perceived hypoglycaemia •	3.0 (2.0-4.0)	1.0 (0.3-1.8)	U=8.0 p=0.021***
General well-being ▲	19.0 (14.0-31.0)	25.0 (12.8-27.5)	U=34.0 p=0.962

*** denotes statistically significant result at α-level of 0.05

□ scored from -3 (extremely bad) to +3 (excellent)

¥ scored from -3 (maximum negative impact) to +3 (maximum positive impact)

◆ scored from -9 (maximum negative impact) to +9 (maximum positive impact)

† scored from 0 to 36, the higher the score, the higher the treatment satisfaction

• scored from 0 to 6, the higher the score, the greater the perceived frequency

▲ scored from 0 to 36, the higher the score, the higher the well-being

4.3 Primary outcomes

Table 3 shows the change in the primary outcomes HbA1c and QoL scores at 6 and 12 months. In Group I at 6 months QoL, as measured by the average weighted impact (AWI) of diabetes on QoL, was significantly improved. Results suggest the improvement may have been sustained through to 12 months but 12 month data failed to reach statistical significance. At 6 and 12 months there were no significant differences within or between Group I and Group D in HbA1c and other measures of QoL. Primary outcome results are described in more detail in the following sections.

Table 3 Primary outcomes baseline through 12 months: differences within and between Group I and Group D.

Values are median (interquartile range) unless otherwise stated.

Variable	Group	Baseline	6 months	12 months	Difference within groups baseline to 6 months	Difference within groups baseline through 12 months	Difference between groups at 6 months
HbA1c (mmol/mol)	Group I n=7	58 (45-66)	53 (40-66)	58 (39-67)	z=-0.679 p=0.563	$\chi^2(2)=0.963$ p=0.680	U=52.0 p=0.109
	Group D n=10	74 (47-81)	69 (49-76)	71 [Ⓜ]	z=-1.585 p=0.121	-	
Present quality of life [Ⓐ]	Group I n=7	1.0 (0-1.0)	1.0 (0-2.0)	1.0 (1.0-2.0)	z=-0.816 p=0.750	$\chi^2(2)=1.50$ p=0.815	U=35.0 p=1.00
	Group D n=10	1.0 (0-2.0)	1.0 (0.8-2.0)	1.5 [Ⓜ]	z=-0.333 p=1.000	-	
Impact of diabetes on quality of life [¥]	Group I n=7	-2.0 (-2.0 - -1.0)	-2.0 (-2.0 - 0)	-1.0 (-2.0 - 0)	z=-1.342 p=0.500	$\chi^2(2)=2.00$ p=0.556	U=40.0 p=0.669
	Group D n=10	-2.0 (-2.3 - -1.0)	-1.0 (-1.5 - -0.8)	-1.5 [Ⓜ]	z=-1.511 p=0.250	-	

[Ⓐ] scored from -3 (extremely bad) to +3 (excellent)

[¥] scored from -3 (maximum negative impact) to +3 (maximum positive impact)

[Ⓜ] n=2, mean value provided

Table 3 (Continued)

Variable	Group	Baseline	6 months	12 months	Difference within groups baseline to 6 months	Difference within groups baseline through 12 months	Difference between groups at 6 months
Average weighted impact of diabetes on quality of life ♦	Group I n=7	-2.8 (-4.5 - -0.8)	-1.6 (-2.9 - -0.4)	-1.0 (-1.7 - -0.6)	z=-2.028 p=0.047***	$\chi^2(2)=6.00$ p=0.051	U=39.0 p=0.740
	Group D n=10	-3.7 (-4.3 - 0)	-1.9 (-3.9 - -0.1)	-2.76 [Ⓜ]	z=-1.244 p=0.250	-	
Weighted impact of diabetes on “freedom to eat as I wish” ♦	Group I n=7	-4.0 (-6.0 - -1.0)	-2.0 (-6.0 - 0)	-2.0 (-9.0 - -1.0)	z=-1.890 p=0.125	$\chi^2(2)=3.90$ p=0.177	U=36.5 p=0.887
	Group D n=10	-4.0 (-7.5 - 0)	-3.0 (-6.0 - 0)	-1.0 [Ⓜ]	z=-0.542 p=0.688	-	
Weighted impact of diabetes on “freedom to drink as I wish” ♦	Group I n=7	-2.0 (-4.0 - 0)	-1.0 (-2.0 - 0)	-1.0 (-9.0 - -1.0)	z=-1.225 p=0.313	$\chi^2(2)=5.00$ p=0.852	U=29.0 p=0.601
	Group D n=10	-4.0 (-6.0 - 0)	-2.0 (-4.0 - 0)	0 [Ⓜ]	z=-0.707 p=0.750	-	

♦ scored from -9 (maximum negative impact) to +9 (maximum positive impact)

[Ⓜ] n=2, mean value provided

*** denotes statistically significant result at α -level of 0.05

4.3.1 HbA1c

HbA1c decreased non-significantly in both Group I and Group D between baseline and 6 months, and in Group I increased back to baseline by 12 months (Figure 4).

The number of participants achieving HbA1c <53mmol/mol in Group I and Group D was equal at baseline (29% and 30% respectively). By 6 months participants achieving HbA1c <53mmol/mol had increased to 57% in Group I whilst remaining constant at 30% in Group D however there was not a significant association between group allocation and achievement of HbA1c <53mmol/mol at 6 months ($p=0.350$).

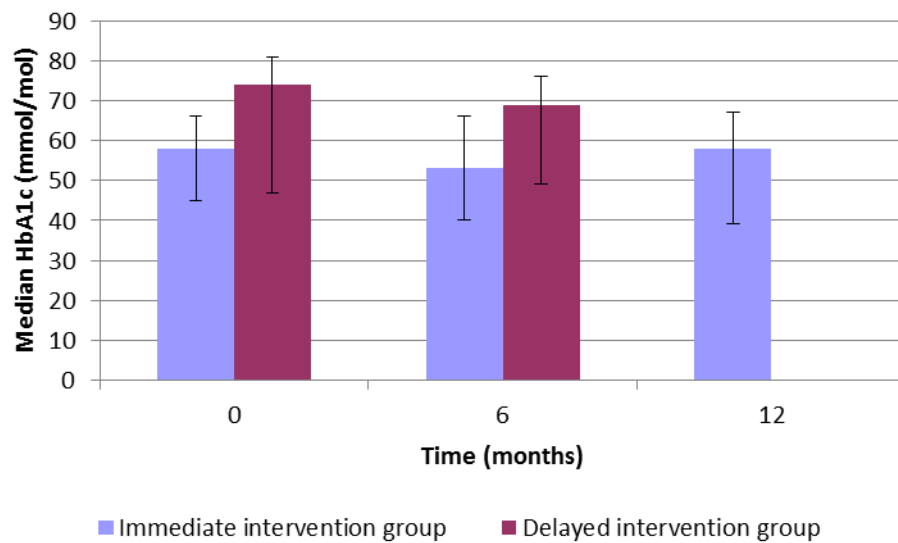


Figure 4 Change in HbA1c baseline to 6 months

4.3.2 Quality of life

Patient-reported present QoL did not change in either group at any time point; impact of diabetes on QoL improved non-significantly in both Group I and Group D (Figure 5). AWI of diabetes on QoL improved in both groups and was significantly improved in Group I at 6, but not 12 months (Figure 6) with a large effect size due to the intervention at 6 months ($r=-0.54$). Perceived dietary freedom improved non-significantly in both groups (Figure 6).

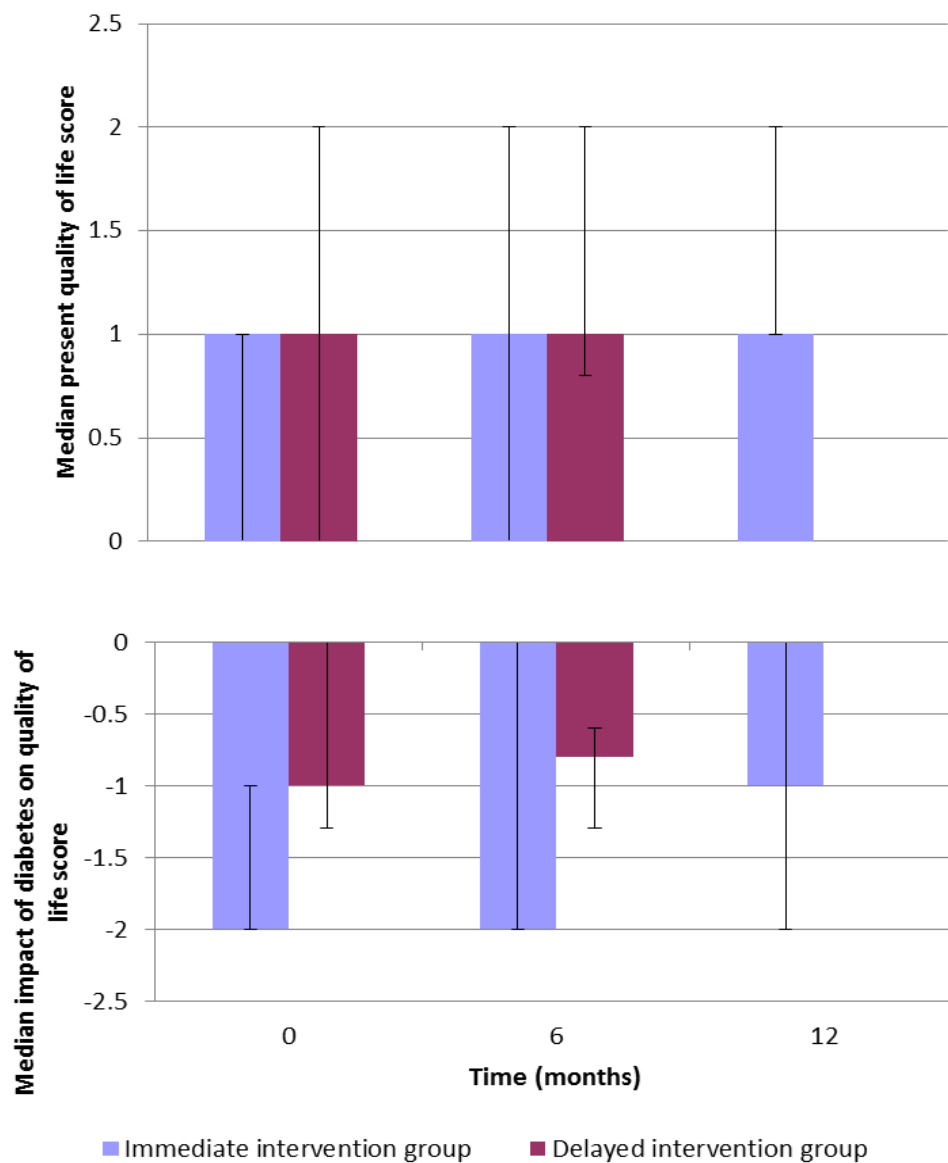
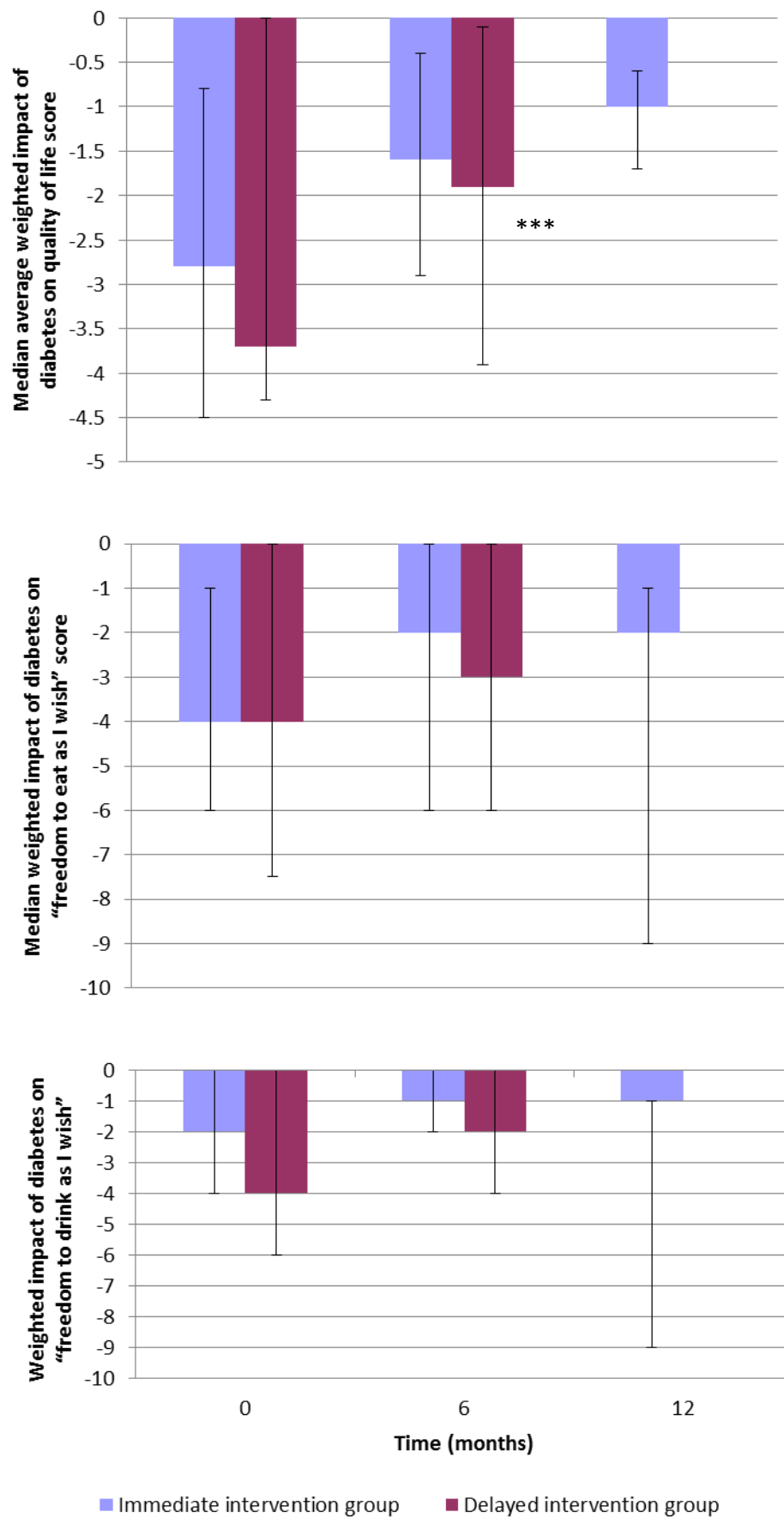


Figure 5 Change in present QoL and impact of diabetes on QoL baseline to 6 months.

Error bars depict the interquartile range.



*** denotes statistically significant result at α -level of 0.05

Figure 6 Change in average weighted impact, “freedom to eat as I wish” and “freedom to drink as I wish” baseline to 6 months. Error bars depict the interquartile range.

4.4 Secondary biomedical outcomes

At 6 months TDI had decreased by a clinically relevant quantity in Group I but there were no significant differences between Group I and Group D for any secondary outcome (Table 4). There was a trend towards reduced waist circumference in both groups, and towards lower diastolic blood pressure in Group D, at 6 months. Total cholesterol increased by a clinically relevant, but non-significant amount at 6 months in Group I, this was accompanied by a small non-significant rise in HDL cholesterol. Episodes of hypoglycaemia were low and no participant experienced severe hypoglycaemia.

In addition the confounding factors alcohol intake and physical activity level did not vary significantly. There was no difference in self-reported alcohol intakes between groups at baseline ($U=40.5$ $p=0.601$) or 6 months ($U=40.0$ $p=0.669$), and no significant change within Group I at 6 months ($z=-0.37$, $p=0.875$) or 12 months ($\chi^2(2)=2.80$, $p=0.278$), nor within Group D at 6 months ($z=-1.35$, $p=0.219$). Alcohol intakes were low on the whole, but variable, with baseline levels (median and interquartile range) in Group I at 0 units/week (0-4.5) and in Group D at 1.4 units/week (0-13.6). There was also no difference in self-reported levels of physical activity between groups at baseline ($p=1.000$) or 6 months ($p=1.000$), and no significant change within Group I at 6 months ($z=0$, $p=1.000$) or 12 months ($\chi^2(2)=0$, $p=1.000$), nor within Group D at 6 months ($z=-1.73$, $p=0.250$). At baseline 29% of all participants classed themselves as sedentary, 47% as lightly active and 24% as moderately active.

Table 4 Secondary biomedical outcomes at baseline through 12 months:

differences within and between Group I and Group D. Values are median (interquartile range) unless otherwise stated.

Variable	Group	Baseline	6 months	12 months	Difference within groups baseline to 6 months	Difference within groups baseline through 12 months	Difference between groups at 6 months
Total daily insulin dose (units)	Group I n=7	84 (42-116)	52 (36-84)	74 (33-160)	z=-0.676 p=0.578	$\chi^2(2)=1.556$ p=0.502	U=38.0 p=0.813
	Group D n=10	71 (48-143)	73 (43-145)	105 [Ⓜ]	z=-0.631 p=0.625	-	
Episodes of hypoglycaemia per month	Group I n=7	1.0 (1.0-3.0)	1.5 (0.5-3.5)	1.5 (0.0-3.5)	z=0 p=1.000	$\chi^2(2)=0.000$ p=1.000	U=26.5 p=0.417
	Group D n=10	0.5 (0.0-4.7)	0.4 (0.0-4.3)	0.5 [Ⓜ]	z=-0.135 p=1.000	-	
BMI (kg/m²)	Group I n=6	31.6 (27.1-34.3)	29.7 (27.4-35.4)	30.1 (27.0-34.4)	z=-0.105 p=1.000	$\chi^2(2)=0.333$ p=0.956	U=40.0 p=0.313
	Group D n=10	33.3 (31.9-35.5)	33.9 (30.9-35.0)	33.1 [Ⓜ]	z=-0.357 p=0.770	-	
Waist circumference (cm)	Group I n=6	118.0 (111.0-121.0)	113.5 (99.4-118.3)	108.5 (102.5-120.5)	z=-1.992 p=0.063	$\chi^2(2)=4.261$ p=0.136	U=43.5 p=0.147
	Group D n=10	118.5 (113.3-127.0)	119.8 (109.9-122.1)	121.0 [Ⓜ]	z=-1.785 p=0.078	-	

[Ⓜ] n=2, mean value provided

Table 4 (Continued)

Variable	Group	Baseline	6 months	12 months	Difference within groups baseline to 6 months	Difference within groups baseline through 12 months	Difference between groups at 6 months
Systolic blood pressure (mmHg)	Group I	133 (100-156)	136 (135-150)	131 (117-143)	z=-0.676 p=0.578	$\chi^2(2)=0.286$ p=0.964	U=21.0 p=0.193
	Group D	133 (123-152)	124 (113-143)	125 [Ⓜ]	z=-1.636 p=0.113	-	
Diastolic blood pressure (mmHg)	Group I	70 (60-79)	72 (57-76)	73 (70-76)	z=0.530 p=0.719	$\chi^2(2)=2.296$ p=0.358	U=29.5 p=0.601
	Group D	76 (67-87)	68 (63-74)	61 [Ⓜ]	z=-1.788 p=0.082	-	
Total cholesterol (mmol/l)	Group I	3.0 (2.7-4.0)	3.5 (2.5-4.0)	3.7 (2.7-4.8)	z=-0.315 p=0.781	$\chi^2(2)=2.846$ p=0.258	U=52.5 p=0.088
	Group D	3.9 (3.6-4.6)	4.0 (3.6-5.0)	4.0 [Ⓜ]	z=-0.672 p=0.523	-	
HDL cholesterol (mmol/l)	Group I	1.0 (0.8-1.2)	1.1 (0.9-1.2)	1.1 (0.9-1.2)	z=-0.138 p=1.000	$\chi^2(2)=0.250$ p=0.928	U=30.5 p=0.669
	Group D	1.1 (0.8-1.2)	0.9 (0.8-1.2)	0.9 [Ⓜ]	z=-1.633 p=0.188	-	
Triglycerides (mmol/l)	Group I	1.4 (1.2-2.8)	1.6 (0.8-2.5)	1.1 (0.8-2.7)	z=-0.841 p=0.469	$\chi^2(2)=1.280$ p=0.558	U=43.0 p=0.475
	Group D	2.3 (1.3-2.9)	2.1 (1.3-3.3)	2.7 [Ⓜ]	z=0 p=1.000	-	

[Ⓜ] n=2, mean value provided

4.5 Secondary psychosocial outcomes

Changes in secondary psychosocial outcomes at 6 and 12 months are shown in Table 5. At 6 months there were no significant differences in the secondary psychosocial outcomes between Group I and Group D. There was a trend towards a reduction in perceived frequency of hypoglycaemia in Group I at 6 months and by 12 months this had reached statistical significance. Conversely there was a trend towards increased perceived frequency of hypoglycaemia in Group D at 6 months. There was also a trend towards improved general well-being in Group I at 6 months, this improvement increased further at 12 months but was not significant.

Participants in Group I were much more satisfied with their diabetes management following carbohydrate counting and insulin dose adjustment training (Figure 7). They also felt they experienced less hyperglycaemia, but scores indicated no perceived change in frequency of hypoglycaemia (median -1.0 and 0, interquartile range -1.0 – 1.0 and -1.0 – 1.0 respectively; scored from -3 [much less now] to +3 [much more now]).

Table 5 Secondary psychosocial outcomes at baseline through 12 months:

differences within and between Group I and Group D. Values are median (interquartile range) unless otherwise stated.

Variable	Group	Baseline	6 months	12 months	Difference within groups baseline to 6 months	Difference within groups baseline through 12 months	Difference between groups at 6 months
Treatment satisfaction†	Group I	28.0 (22.0-36.0)	31.0 (28.0-35.0)	30.0 (30.0-35.0)	z=-1.572 p=0.156	$\chi^2(2)=1.000$ p=0.653	U=24.5 p=0.315
	Group D	25.0 (23.0-29.0)	29.0 (24.0-34.0)	27.5 [‡]	z=-1.620 p=0.188	-	
Perceived hyper-glycaemia •	Group I	2.0 (2.0-5.0)	2.0 (2.0-4.0)	2.0 (2.0-4.0)	z=-0.828 p=0.563	$\chi^2(2)=2.375$ p=0.457	U=29.5 p=0.601
	Group D	2.0 (0-4.0)	2.0 (1.8-3.3)	2.0 [‡]	z=-0.343 p=0.844	-	
Perceived hypo-glycaemia •	Group I	3.0 (2.0-4.0)	2.0 (0-2.0)	1.0 (1.0-2.0)	z=-2.060 p=0.063	$\chi^2(2)=8.435$ p=0.008***	U=46.5 p=0.114
	Group D	1.0 (0.3-1.8)	3.0 (1.0-4.0)	1.5 [‡]	z=-1.597 p=0.094	-	
General well-being ▲	Group I	19.0 (14.0-31.0)	22.0 (18.0-32.0)	24.0 (18.0-33.0)	z=-1.992 p=0.063	$\chi^2(2)=1.000$ p=0.640	U=33.0 p=0.887
	Group D	25.0 (12.8-27.5)	25.0 (18.0-29.3)	27.0 [‡]	z=-1.672 p=0.109	-	

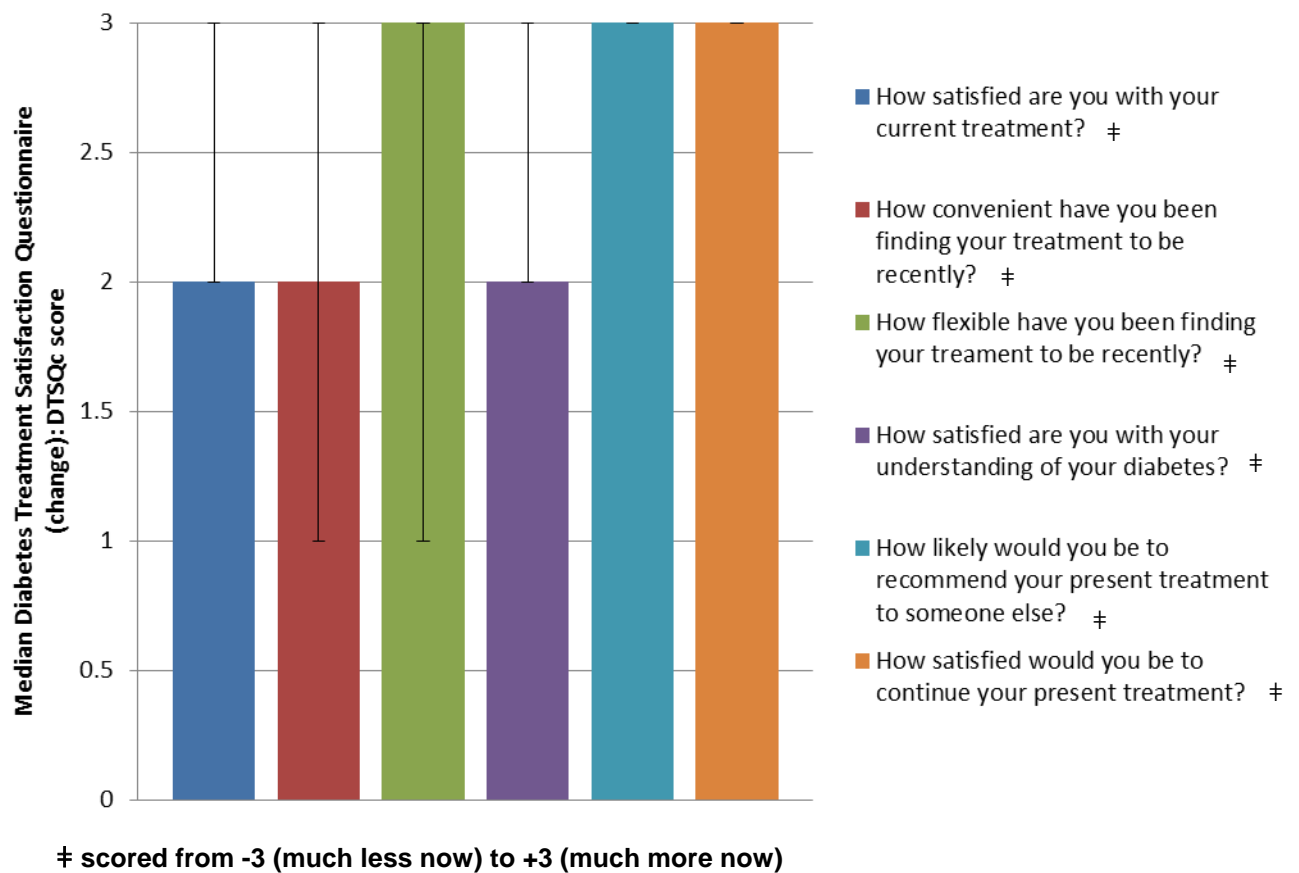
*** denotes statistically significant result at α -level of 0.05

† scored from 0 to 36, the higher the score, the higher the treatment satisfaction

• scored from 0 to 6, the higher the score, the greater the perceived frequency

▲ scored from 0 to 36, the higher the score, the higher the well-being

[‡] n=2, mean value provided



**Figure 7 Diabetes Treatment Satisfaction Questionnaire (change):
treatment satisfaction results for Group I at 6 months.**

Error bars depict interquartile range.

5. Discussion

5.1 Summary of main results

This research indicates that carbohydrate counting and flexible insulin dosing is feasible in adults with T2DM on basal-bolus insulin. MATCH IT education, compared with standard care, resulted in a statistically significant improvement in quality of life at 6 months enabling rejection of the null hypothesis that QoL is not affected by carbohydrate counting and flexible insulin dosing. It was also associated with a significant reduction in perceived frequency of hypoglycaemia at 12 months and there was a trend towards improved general psychological well-being whilst individuals continuing to receive standard care reported a trend towards greater perceived hypoglycaemia.

HbA1c decreased non-significantly in both the immediate and delayed intervention group at 6 months, without a notable increase in actual episodes of hypoglycaemia. It was not possible to reject the null hypothesis that HbA1c is unaffected by carbohydrate counting and flexible insulin dosing. Participants in Group I had lower total daily insulin doses (TDI) at 6 months compared with baseline, but this was a non-significant decrease, whereas participants in Group D had no marked change in TDI. There was no significant increase in BMI and waist circumference in Group I despite increased dietary freedom however there was a clinically relevant but non-significant increase in total cholesterol in Group I.

5.2 Participants

The number of participants recruited into the study was within the projected range. Implications of the uptake and drop-out rates are considered here with respect to clinical practice.

The MATCH IT drop-out rate was high at 53% and only nine participants provided data at all three time-points. A significantly greater proportion of the participants that left the study early dropped out of Group D, the delayed intervention group, compared to Group I, the immediate intervention group. Due to the small sample size, it is possible this occurred by chance. The demographic profile of the participants revealed they were generally older adults with diabetes complications and other pre-existing medical conditions which resulted in poor health preventing continuation in the research for some participants.

Alternatively a greater attrition rate in the delayed start arm of the study could indicate that providing a timely response is important to engage this population in diabetes education. One model of health behaviour proposed by Prochaska and DiClemente (1982) identifies several stages of readiness to change that flow cyclically. Participants may have consented to contribute to the study when they were motivated to improve their diabetes control and a 6 month wait to commence the education resulted in, or coincided with, a change in their motivation levels.

Of the participants that dropped out of the study, 40% dropped out of the study post education suggesting that improved knowledge may not be a significant factor in increasing readiness to change. However the larger proportion (60%) dropped out before commencing the educational intervention signifying the intervention was not likely to be the cause for study withdrawal. This may suggest a contrast to other evidence in T2DM which demonstrated higher drop-out rates in the carbohydrate

counting and insulin dose adjustment arms of the study (Bergenstal et al., 2008). This highlights the intensive nature of this diabetes management method, plus the numerical and analytical skills required, and therefore its unsuitability for some individuals. Often more complex medication regimes result in poorer adherence to treatment (Donnan, MacDonald, & Morris, 2002). Nevertheless in the present study this may not have been as much of a barrier to study completion as in other research populations. This could be explained by MATCH IT participants being drawn from the relatively affluent Cheshire area, which may denote higher educational attainment and less social deprivation (Western Cheshire Primary Care Trust, 2007) and the involvement of self-selected motivated individuals, although the latter is the case with any research.

In clinical practice, it could be expected that a proportion of adults with T2DM would decline this management method, or be deemed unsuitable, due to intensity of personal input. However just under half of the individuals invited to take part in this research project accepted, suggesting that many adults with T2DM currently on standard basal-bolus insulin regimes would consider learning how to adjust their own insulin. MATCH IT uptake may also not represent uptake in a real clinical setting as some individuals preferred not to participate in the project due to its experimental nature, rather than the diabetes management method proposed.

In summary patients should be carefully selected for carbohydrate counting and flexible insulin dosing education as levels of commitment and motivation are required to be high to successfully utilise this method, and inappropriate patient selection could result in wasted resources if individuals are unable or unwilling to employ the technique. Furthermore these results suggests that waiting lists for interventions such as carbohydrate counting and insulin dose adjustment training should be kept short, to at least less than 6 months, and if possible self-referrals be utilised, to ensure engagement with participants at an appropriate time in their motivation levels.

5.3 Primary outcome: HbA1c

5.3.1 *HbA1c results*

Glycaemic control, as represented by HbA1c, improved in both in Group I and Group D at 6 months; these changes were not statistically significant. Achieving a reduction in HbA1c is more challenging when glycaemic control is already close to optimal as the risk of hypoglycaemia is increased and there is less potential to affect glucose excursions from normoglycaemia. Therefore the reduction from a median HbA1c of 58mmol/mol to 53mmol/mol in Group I is more notable than the reduction from 74mmol/mol to 69mmol/mol in Group D at 6 months. This is reflected in the reduced perception of hyperglycaemia compared to past diabetes management in Group I at 6 months, and also in the greater increase in individuals achieving a HbA1c <53mmol/mol in Group I compared to Group D, however the latter should be interpreted in light of some Group I participants' pre-existing proximity to this target.

5.3.2 *Interpretation of HbA1c results*

The reason HbA1c improved in both the control and intervention group is unclear. Participants were excluded if anti-diabetic medication was altered during the study; this did not occur and therefore pharmacological agents cannot account for this difference. Other confounding factors, BMI, self-reported physical activity level and alcohol intake, also did not significantly alter but some determinants of glycaemic control not measured, such as dietary composition and glycaemic index of carbohydrates, may have contributed to these results. It is possible that study participation alone may have resulted in improved glycaemic control in either, or both, arms due to increased consciousness of health decisions and improved support and motivation provided by an increased frequency of appointments with a healthcare professional. Furthermore

as individuals in Group D were aware of the nature of the study, they may have deliberately or unconsciously standardised their carbohydrate intake.

Another element introducing variability in response to MATCH IT may have been in disparities in the use of this management technique. A reduction in HbA1c in T1DM as a result of carbohydrate counting training derives from a number of behaviours, not just matching insulin to carbohydrate load but also prompt and appropriate treatment of hypoglycaemia, correct timing of insulin doses and adjusting insulin for exercise and alcohol. The difference in the frequency of display of these behaviours has been associated with up to a 10mmol/mol difference in HbA1c in adults with T1DM who adjust their insulin (Delahanty & Halford, 1993).

The DAFNE Study Group (2002), in the same study design as the current research, found that HbA1c decreased from 79mmol/mol to 68mmol/mol in adults with T1DM who were trained in carbohydrate counting and insulin dose adjustment. This reduction of 11mmol/mol in HbA1c is greater than the 5mmol/mol reduction observed in both Group I and Group D in the present study. However a decrement of 5mmol/mol remains a notable clinical outcome and is associated with a 15-20% risk reduction for diabetes-related complications (UKPDS Group, 1998). Moreover HbA1c does not provide detail about glucose variability; it may be proposed that MATCH IT has the potential to improve glucose excursions in the post-prandial period more than other insulin regimes. As post-prandial glucose excursions are more closely associated with CVD risk than fasting glycaemia (Horton, 2009), MATCH IT may have an enhanced capability in diabetes-related macrovascular disease prevention.

5.3.3 Physiology of mechanisms of impact

No conclusive evidence demonstrates the impact of carbohydrate counting and insulin dose adjustment on glycaemic control; whether this study failed to demonstrate a significant effect due to a genuine lack of association or on methodological grounds

cannot be surmised. Carbohydrate counting and insulin dose adjustment could have a different outcome in T2DM compared to T1DM for several reasons. Firstly HbA1c may not have as much potential to decrease for adults with T2DM who carbohydrate count compared to those with T1DM who do so. Some individuals with T2DM are capable of a greater degree of physiological regulation of blood glucose levels as a result of residual endogenous insulin production thereby limiting the impact of flexible insulin dosing. For others with little remaining pancreatic β -cell function, the effect on glycaemic control may be conjectured to be similar to T1DM. Alternatively this diabetes management method could have a greater impact on glycaemic control in T2DM, with less accuracy in carbohydrate counting necessary to achieve this, as endogenous insulin may assist in attenuation of glycaemic variability.

Moreover interpretation of MATCH IT results is complicated by emerging evidence that some prandial insulins have a reduced hypoglycaemic effect and delayed action in obese individuals with T2DM due to decreased adipose tissue blood flow and larger insulin doses (Gagnon-Auger et al., 2010). This provides an additional possible mechanism for limited efficacy in reducing post-prandial hyperglycaemia compared to T1DM, irrespective of carbohydrate load matching. It is also possible that the pharmacokinetics and pharmacodynamics of prandial analogue insulin aspart, lispro and glulisine, used by participants in this study, are affected differently in response to both obesity and T2DM (Barnett, 2006). Unfortunately the present study is unable to elucidate the complex relationship between the effect of carbohydrate counting and insulin dose adjustment, endogenous insulin production, obesity and choice of prandial insulin. Adults with T2DM represent a diverse group which could result in a heterogeneous response to flexible insulin dosing and it is possible only a subset of individuals with T2DM would benefit from this management approach.

5.3.4 Comparison with existing literature

Comparison with the DAFNE study is limited by the different participant population, and as a less intensive education programme was used in MATCH IT (5 full days versus 2 half-days respectively). Additionally the types of insulin used by participants in the DAFNE trial are not disclosed; older isophane long-acting insulin and soluble prandial insulin, with different activity profiles than newer analogue long-acting and prandial insulins, were likely utilised to a greater degree than in the present study. Prandial analogue insulin lispro and insulin aspart are both associated with lower post-prandial blood glucose levels and lower HbA1c than soluble insulins (Anderson et al., 1997; Raskin, Guthrie, Leiter, Riis, & Jovanovic, 2000) which means the 11mmol/mol HbA1c reduction accounted for by flexible insulin dosing in the DAFNE study, and the 5mmol/mol reduction in the present study discussed earlier should be compared with caution.

The results of this study for improved glycaemic control are consistent with results from existing literature on carbohydrate counting and flexible insulin dosing in T2DM however cannot be definitively attributed to this technique due to improved glycaemic control in the control group. Compared to the present study, Bergenstal et al. (2008) found no difference in the drop in HbA1c resulting from training adults in carbohydrate counting, or use of a simple titration algorithm, at 17mmol/mol and 16mmol/mol respectively. Results are not directly comparable as Bergenstal et al. (2008) initiated basal-bolus insulin in some participants whereas this research included only individuals already using a basal-bolus insulin regime for at least six months. Transfer from an ineffective insulin regime to a basal-bolus regime, together with a titration schedule, will undoubtedly cause a drop in HbA1c independent of carbohydrate counting and flexible insulin dosing, thereby accounting for the discrepancy between observed results in the two studies as glycaemic improvement is only partly attributable to carbohydrate counting and insulin dose adjustment training in Bergenstal et al.'s study (2008).

Additionally the cohort of participants in Bergenstal et al.'s study (2008) had a mean age of 55 years, a notable difference from the median age of 66 and 61 years in the intervention and control group of this study respectively. Younger adults can have very variable diets (Huang, Song, Schemmel & Hoerr, 1994) therefore commencing flexible insulin dosing in a slightly younger group of individuals could have a greater degree of impact upon glycaemic control than in an older group with more established eating patterns.

5.3.5 Significance of results

Overall optimal glycaemic control was not achieved by adults with T2DM who were carbohydrate counting and insulin dose adjusting in this study. Only 57% of participants achieved a HbA1c <53mmol/mol, arguably an appropriate individualised target for this population (Inzucchi et al., 2012). As research participants may be assumed to be a more motivated patient group it is disheartening that despite maximal diabetes pharmacological treatment and insulin adjustment only a small number achieved the recommended target. This is a widespread issue; nearly three-quarters of all adults with T2DM, and nearly two-thirds of adults with T2DM on insulin, fail to achieve a glycaemic target of <48mmol/mol (Health and Social Care Information Centre, 2012; Holman et al. 2009). Although it is acknowledged this target is likely inappropriate for some, this demonstrates the challenges of attaining desirable blood glucose levels for all.

In short, for some individuals with T2DM carbohydrate counting and flexible insulin dosing may have a glycaemic advantage over a standard insulin regime but this remains only an enhancement to an imperfect therapy. It is clear that more advanced treatment options to assist these individuals achieve near-normal glycaemia are required; research continues into promising alternatives and additions to current

treatment such as GLP-1 analogues, bolus insulin advisor meters and closed loop insulin pumps. .

5.4 Primary outcome: Quality of life

Compared to standard care, carbohydrate counting and insulin dose adjustment training resulted in a statistically significant improvement in QoL at 6 months, and a trend towards improved general well-being. Although not a primary outcome, the significance of general well-being, representing not just health-related quality of life, is also discussed within this section.

On the whole, both the intervention and control group had improved median scores in the separate measures of QoL, which may have arisen by chance due to the small sample size, or have occurred simply as result of participating in the research and a greater sense of engagement with their health status, or improved knowledge without change in behaviour. As in other studies QoL improvements may not reach a level of significance until 12 months or beyond (DAFNE Study Group, 2002) suggesting a longer monitoring period may be necessary to fully appreciate changes in QoL. Baseline QoL scores were similarly low in the MATCH IT and DAFNE studies (DAFNE Study Group, 2002), and are consistent with other similar research (Mujika-Zabaleta, Forbes, While, Mold & Canga, 2010) . As individuals with the lowest QoL gain the most from carbohydrate counting and insulin dose adjustment (Byrne et al., in press), it could be proposed that MATCH IT would have a comparably positive impact to the DAFNE study. The following discussion will demonstrate that this was not exactly the case.

The average weighted impact (AWI) on diabetes score that showed a significant change in Group I at 6 months represents the accumulated score of nineteen different QoL domains including freedom to eat and drink. The domain “Freedom to eat as I wish” showed improvement from baseline through to 12 months in both groups but a

greater improvement was seen in Group I. However as it did not change significantly, but the AWI score did, in conjunction with the trend towards improved general well-being, this suggests greater improvements in QoL are occurring in areas other than dietary liberality. Interestingly dietary freedom is usually found to be the aspect of QoL most negatively impacted by diabetes (Bradley et al., 1999) and was therefore the aspect that improved most dramatically following DAFNE training (DAFNE Study Group, 2002). This is in contrast to MATCH IT results, perhaps because individuals with T2DM do not suffer the consequences of dietary lapses or misjudgements, the hyper- or hypoglycaemia, to the same degree that adults with T1DM do. Therefore despite carbohydrate counting and flexible insulin dosing appearing to relate predominantly to dietary freedom, in this study it clearly had a far-reaching positive impact on individuals' lives. Emerging evidence may also provide an additional possible mechanism for improved QoL independent of dietary freedom. In a small pilot study, Penckofer et al. (2012) demonstrated a reduced QoL and negative moods in the presence of greater glycaemic variability. Although glucose excursions were not measured explicitly, MATCH IT data suggests attenuation of glycaemic variability through improvement or maintenance of HbA1c without increased incidence of hypoglycaemia.

Finally it is important to highlight that MATCH IT did not to have a negative effect on participants' QoL despite the increased focus on their medical condition, encouragement to perform home blood glucose monitoring more frequently, more daily insulin injections and the impact of scrutinising their dietary intake. It has been demonstrated that treatment intensity may decrease QoL (Wexlar et al., 2006) therefore elements of this management method must be negating this effect in both T1DM and T2DM.

Increased self-efficacy, the confidence in personal ability, is highly likely to be the factor underlying the observed association of increased patient input into personal health without deterioration of QoL and general well-being seen in the MATCH IT study. Low self-efficacy is related to low levels of diabetes-related QoL and poorer self-management (Glasgow, Toobert, & Gillette, 2001). Likewise high self-efficacy is associated with greater adherence to health recommendations and better self-management (Aljaseem, Peyrot, Wissow & Rubin, 2001). Self-efficacy is the key to a positive feedback system that perpetuates enhanced self-management and QoL thereby improving glycaemic control and reducing risk of diabetes-related complications. Bradley and Gamsu (1994) further emphasise the close link between day-to-day QoL and blood glucose regulation as improving psychological well-being reduces stress hormone production resulting in more manageable blood glucose levels and, cyclically, improving glycaemic control enhances QoL by causing less anxiety regarding home blood glucose monitoring readings. Additionally diabetes knowledge and self-care behaviour are generally poorly correlated (Knight, Dornan, & Bundy, 2006). MATCH IT, and similar interventions such as DAFNE, may be successful because they combine educational approaches with knowledge and behaviour components. They provide the reason for behaviour changes, such as knowledge about macronutrient effects on glycaemia, and provide the training and support to implement behaviours to utilise the new knowledge thereby substantially increasing users' self-efficacy and resulting in both improved biomedical outcomes as well as patient-reported outcomes.

It is now widely accepted that improved medical outcomes are not the only goal of healthcare interventions. The UK Government are committed to empowering people with chronic diseases (including diabetes) to take an active role in their own health care (Department of Health, 2010). Courses to enable chronic disease self-management are commonplace and are associated with improved self-efficacy, fatigue, anxiety,

depressed moods and health distress (Barlow, Wright, Turner & Bancroft, 2005) which contribute to overall quality of life. Similarly the National Service Framework for Diabetes (Department of Health, 2001), promotes fostering patients' self-efficacy to optimally manage diabetes. The present study is in line with these current national recommendations.

Again definitive conclusions about overall impact of carbohydrate counting and insulin dose adjustment training on QoL cannot be drawn from the present small study but individuals with T2DM already experience lower QoL than their peers (Holmes et al., 2000) therefore any management methods that mitigate this reduction in QoL, as MATCH IT appears to, whilst not associated with a deterioration in glycaemic control, are of considerable value.

5.5 Secondary outcomes

5.5.1 *Hypoglycaemia*

There was a trend towards a reduction in perceived frequency of unacceptably low blood glucose levels, measured by the DTSQ, at 6 months in Group I, and by 12 months this had reached statistical significance. However this data is contradicted by the DTSQc results in Group I at 6 months which signify participants discerned no difference in incidence of hypoglycaemia when comparing their current and past diabetes management. Actual frequency of hypoglycaemic episodes was very low in both groups at all time-points, and comparable with other studies (Holman et al., 2007). No participants experienced severe hypoglycaemia either before or during the study. The number of reported hypoglycaemic episodes interestingly increased slightly in Group I at 6 months, although this was neither clinically relevant nor statistically significant and therefore could have occurred by chance. Likewise an increase in mild hypoglycaemia occurred in the carbohydrate counting arm of Bergenstal et al.'s study

(2008). Other possible reasons for the divergence in perceived and actual hypoglycaemia are discussed below.

At baseline perceived frequency of unacceptably low blood glucose levels were significantly different in the two groups, with Group I feeling they experienced greater frequency of hypoglycaemic episodes than Group D. This could represent a greater anxiousness about hypoglycaemia in Group I which caused there to be an over-representation of perceived hypoglycaemia incidence in the treatment satisfaction questionnaire, which when quantified, did not correspond to a greater self-reported frequency of hypoglycaemia. Alternatively the method of identifying frequency of hypoglycaemic episodes was limited to self-reporting which may not have been sensitive enough to show a genuinely greater number of hypoglycaemic episodes occurring in Group I. The reliability of retrospective recollection of hypoglycaemic episodes has not been explored in type 2 diabetes but literature in T1DM suggests collection of information about frequency of mild hypoglycaemic episodes over a week after their occurrence can be prone to significant recall bias (Pedersen-Bjergaard, Pramming & Thorsteinsson, 2003). This may also explain the contradictory results regarding perceived frequency of hypoglycaemia in the DTSQ and DTSQc; the DTSQ data is likely to be more robust. Therefore a more rigorous method of ascertaining blood glucose levels, for example periods of intensive monitoring accompanied by collection and analysis of all blood glucose values, could be used in a larger scale study and clarify the relationship between perceived and actual hypoglycaemia.

A further explanation for the discrepancy could be the interpretation of the question in the DTSQ questionnaire "How often have your blood sugars been unacceptably low?" It is possible that the reassurance of the ubiquitousness of hypoglycaemia, attained from the interaction with group members, or the provision of information about glycaemic targets, has caused an alteration in what participants saw as an

unacceptably low blood glucose level at baseline compared to at 6 months. Moreover an increased sense of control over blood glucose levels could have decreased the perception of hypoglycaemia as it may have reduced a sense of helplessness surrounding hypoglycaemia if participants could attribute it to inappropriate insulin dosing for a carbohydrate load and/or activity.

A reduction in perception of hypoglycaemia, even whilst incidence of hypoglycaemia does not change, is a beneficial outcome as it could represent improved coping with hypoglycaemia or increased understanding of the causes of hypoglycaemia which may leave the participant feeling better equipped to deal with, or prevent, hypoglycaemia. Hypoglycaemia and anxiety about hypoglycaemia in T2DM reduces QoL (de Grauw, Van de Lisdonk, Van Gerwen, Van den Hoogen & Van Weel, 2001; Irvine, Cox & Gonder-Frederick, 1992) plus has an impact on mortality and morbidity and can have substantial financial implications (Amiel, Dixon, Mann & Jameson, 2008). Risk of hypoglycaemia increases with intensification of treatment targets (Turner et al., 1998) therefore the lack of an increased rate of hypoglycaemia and reduced perception of hypoglycaemia in this study attests to the success of carbohydrate counting and flexible insulin dosing in providing a physiologically appropriate insulin dose.

5.5.2 Total daily dose of insulin

Total daily insulin dose (TDI) was decreased following MATCH IT education in Group I at 6 and 12 months, and increased in Group D at 6 months but no changes in this variable were significant. TDI is of interest as a proxy measure of appropriate insulin dosing; if TDI remains constant or decreases without significant deterioration of HbA1c, as occurred in Group I at both 6 and 12 months, it suggests that insulin provision has become optimised and dosing is occurring at physiologically appropriate times. This is subject to the confounding effects of changes in BMI, waist circumference and activity levels as insulin requirements vary in part due to body weight and insulin resistance

(De Fronzo, 2004). Activity levels did not significantly change in either group however BMI and waist circumference did decrease non-significantly in Group I. The reductions in TDI, BMI, waist circumference and HbA1c in Group I are inter-related; change in any one variable will likely influence the other two with causality being difficult to ascertain. An alternative explanation could be that better glycaemic management diminished glucose toxicity arising from hyperglycaemia in pancreatic β -cells, hence promoting insulin production and resulting in reduced exogenous insulin requirements (Leahy & Pratley, 2011).

Many participants expressed a desire to lose weight during personal communication throughout the MATCH IT sessions. A reduction in TDI and flexible insulin dosing could produce unintentional weight loss through a reduction in the anabolic effect of insulin, reduction in hunger induced by subclinical over-insulinisation or a lower frequency of hypoglycaemia necessitating consumption of additional energy to correct blood glucose levels. Conversely flexible insulin dosing may have enabled participants to deliberately reduce their energy intake without concern about hypoglycaemia, or the motivation provided by health professional contact may have elicited dietary changes. The potential positive outcomes suggested by these results are unable to be fully interpreted with the existing data. Future research could involve both qualitative data to ascertain thoughts and feelings associated with this diabetes management method, and quantitative data on nutrient intakes and hunger levels.

A lack of increase in TDI over 12 months is further notable as progression of β -cell failure in T2DM results in a tendency for insulin doses to increase over time in order to maintain stable glycaemic control (Holman et al., 2009). Future studies would benefit from including a measure of endogenous insulin production, such as serum C-peptide, to reduce confounding for associations of TDI.

Robust data regarding the change in TDI is imperative for cost effectiveness analyses of this management method for T2DM. Reducing TDI, even to a small degree, would have an economic implication. In the financial year 2011/12 more money was spent on drugs for diabetes than any other group of medications (Health and Social Care Information Centre, Prescribing and Primary Care Services, 2012). Incorporation of carbohydrate counting and insulin dose adjustment training into routine care for T2DM would only be advocated if evidence indicated not only improvements in clinical and psychological parameters, but a positive cost-benefit therefore this should also be a priority of further research.

5.5.3 *Treatment satisfaction*

Treatment satisfaction remained approximately static in Group I whilst increased slightly and non-significantly in Group D during the MATCH IT study. Again improved satisfaction with healthcare may have occurred simply as a result of participating in the trial and it may be that not all changes in satisfaction were able to be detected.

Treatment satisfaction scores in both groups were high at baseline indicating a pre-existing high degree of satisfaction and thus limiting possible improvements. The DTSQc questionnaire was designed to overcome this “ceiling effect” (Pouwer, Snoek, & Heine, 1998). Data from the DTSQc show MATCH IT resulted in a considerable increase in treatment satisfaction at 6 months which was not detected by the DTSQ; carbohydrate counting and flexible insulin dosing therefore appears to be a well-accepted management option for adults with T2DM. DTSQc results are not comparable between or within groups therefore inferential statistics were not possible. This data serves to substantiate the notion that changes in treatment satisfaction are not observed because participants are already satisfied with their treatment at baseline, rather than because improvements did not occur.

5.5.4 Vascular risk factors: BMI and waist circumference

Vascular disease is the biggest cause of mortality and morbidity in T2DM (Roper, Bilous, Kelly, Unwin & Connolly, 2001). It is therefore crucial that any gains in terms of glycaemic control and quality of life that may be achieved with MATCH IT training in T2DM are not offset by deterioration in the vascular risk factors BMI, waist circumference, blood pressure and blood lipids. This is particularly relevant to the present study as insulin regimes including prandial doses of insulin are associated with greater weight gain than pre-mixed or basal insulin regimes (Holman et al., 2007) which could then induce increments in other CVD risk factors.

In this research participants were educated in carbohydrate counting as a means of liberating as opposed to restricting dietary intake. Healthy eating was advocated as a principle throughout but no specific guidance on what constitutes healthy eating was provided. It is with interest that anthropometric data is here examined as adults with T2DM are typically prone to overweight and being overweight likely contributed to the development of their T2DM through insulin resistance (Taylor, 2008). This could suggest that allowing increased dietary freedom, by providing the means of blood glucose management regardless of carbohydrate intake, and the knowledge that dietary fat has a negligible effect on short-term glycaemic control, could result in exacerbation of already elevated BMI and waist circumference in this cohort, particularly in association with the weight gain risk of prandial insulin doses (Holman et al., 2009). In fact BMI and waist circumference both decreased non-significantly in the intervention group at 6 months. As previously discussed this could suggest that participants improved their eating habits, or the flexibility of the current approach allowed variable, and perhaps reduced, carbohydrate portions, or perhaps that reduced insulin doses caused weight loss. This is especially notable considering glycaemic control improved, a consequence of which is usually weight gain secondary to decreased glycosuria.

Unfortunately the improvement in BMI and waist circumference may have been a temporary consequence of participating in a research trial causing greater consciousness of food choices as the improvement is attenuated slightly, though still persists, at 12 months. On the other hand BMI and waist circumference increased slightly in the control group at 6 months despite participating in the study, although healthcare professional contact time was not matched with the intervention group. This could represent a lack of change in eating habits in this group due to reduced time spent with research staff hence less inadvertent motivation for improved eating behaviours, or that the continuation of rigid insulin dosing has limited weight maintenance.

Regardless of the causal factors, carbohydrate counting and flexible insulin dosing appears to be associated with weight loss in a population group prone to obesity.

5.5.5 Vascular risk factors: Blood pressure and blood lipids

Blood pressure and blood lipids again represent risk factors for vascular disease and may have been susceptible to increases in the intervention arm of this study, both due to increases in body weight and to enhanced dietary freedom. Blood pressure did not change in Group I but decreased non-significantly in Group D over 6 months.

Total cholesterol was increased compared to baseline in Group I at both 6 and 12 months however this was not significant and cholesterol remained well-controlled. This was accompanied by a small non-significant rise in HDL cholesterol but not sufficient to account for the elevation in total cholesterol indicating atherogenic LDL increases were responsible for the overall rise in total cholesterol. Although cholesterol has not been shown to increase in some studies of carbohydrate counting (Bergenstal et al., 2008; DAFNE Study Group, 2002), one study, in line with MATCH IT demonstrated that

increased liberalisation of diet was associated with increased cholesterol (Mühlhauser et al.,1995).

5.6 Strengths

This proof-of-concept study was small but well-designed with appropriate methodology, and utilises an educational approach that would be viable in routine clinical practice. The use of randomisation and a control group adds valuable internal validity and although a limited number of participants were involved, the consistency of the results with comparable research, even those that did not reach statistical significance, lends weight to the conclusions regarding the primary outcomes reached. Data were handled sensitively taking sample size, skewed variables and outliers into consideration through the use of non-parametric tests, and medians and interquartile ranges as measures of centrality and dispersion. In addition external validity was good as the study population likely represents the target population of older adults with T2DM in Cheshire. It was acknowledged at the outset that this study was underpowered meaning there may be associations which were not able to be detected yet this does not undermine the statistically significant results that were established.

5.7 Limitations

5.7.1 Study design and sample size

As this piece of research was carried out for a Master's degree project it was constrained in duration and sample size. Firstly the small sample size necessary to make this study manageable results in several limitations, however it also made the project well suited as a pilot study. Although the small sample size limits extensive hypothesis testing, information has been gained from which sample sizes for future research in this area could be calculated. Data presented here are exploratory; the

study was underpowered to detect significant changes to glycaemic control and psychosocial outcomes and the sample size does increase the likelihood of a “type II error” occurring as a result of the study’s lack of power.

The drop-out rate was also high, likely due to the demographic of the study population and duration of the study, further reducing the sample size such that inadequate data was collected at the 12 month point for Group D. Moreover the small sample size resulted in baseline differences between the control and intervention groups despite randomisation. Notable disparities included a significantly higher perceived frequency of hypoglycaemia, and a non-significantly lower general well-being and lower HbA1c in Group I. This implies Group I may have comprised more “worried well” individuals, or that maintaining better glycaemic control was having negative effects on well-being, perhaps due hypoglycaemia, and therefore Group I had more to gain in the MATCH IT study. In sum, the inequalities in baseline variables made results more challenging to interpret.

A second limitation is that the study was only one year in duration and long-term follow-up would be required to fully ascertain effects on biomedical and psychosocial parameters as similar studies acknowledge deterioration of glycaemic benefits over time and suggest refresher courses may be required to maintain beneficial effects of the interventions (Plank et al., 2004; Speight et al., 2010). Expanding the data collected for this study would also have enhanced its utility but was not possible. Options could include details of qualitative experiences during MATCH IT, 8-point glucose profiles and plasma C-peptide.

It is acknowledged that detection bias will have compromised the internal validity of this research as it was not possible to blind either researcher or participants to their group allocation. This may have affected outcomes that required some degree of subjective interpretation, for example physical activity levels, incidence of hypoglycaemia and all

questionnaire answers. Additionally lack of blinding could also have attenuated the difference between groups as participants were informed of the nature of the study investigating matching insulin doses and carbohydrate intakes and therefore may have become more aware of their carbohydrate loads relative to their static insulin doses. Data collection techniques may also have contributed to decreased internal validity and reliability as laboratory assays are subject to low inherent error, and the method for assessing actual incidence of hypoglycaemia was limited due to reliance on participant recall, as previously discussed. Data on physical activity levels was also not as robust as other outcomes, relying on subjective reporting, to control for confounding.

Finally group education for individuals using basal-bolus insulin, in the absence of carbohydrate and flexible insulin dose training, has been associated with improved HbA1c, mostly as a function of improved diabetes knowledge (Schiel, Ulbrich & Müller, 1998) although increased diabetes knowledge is not always associated with better biomedical outcomes (Persell et al., 2004). In this study the disparity in health professional contact time and general diabetes knowledge provision between the intervention and control groups could have contributed to the observed results. The group education approach on which MATCH IT was based on has been shown to be effective at improving HbA1c in individuals with T1DM (DAFNE Study Group, 2002; Patel et al., 2010) however individuals' learning styles vary. Some participants may have responded better to individual educational sessions, or to gradual rather than intensive education. It cannot be dismissed that a lack of significant changes in biomedical and psychosocial outcomes could be due to the education method rather than the diabetes management technique.

5.7.2 Sample composition

Inherent in almost any research is a selection bias arising from the inclusion of potentially more health-motivated participants which could exaggerate the effect of the

intervention studied. Similarly attrition bias may have occurred in the difference between study completers and those who dropped out at baseline. Results may not be generalisable to individuals with T2DM in other areas as the geographical area from which MATCH IT sampling occurred is more affluent than the UK average (Western Cheshire Primary Care Trust, 2007), and the sample included no heterogeneity in ethnic group or age. Insulin therapy choice may further limit generalisability of results. Most MATCH IT participants used insulin glargine or detemir as long-acting background insulin however in current practice many adults with T2DM newly commenced on a basal-bolus insulin regime will be prescribed isophane insulin. Systematic reviews have shown the non-inferiority of isophane insulin compared to over glargine and detemir in T2DM (Qayyum et al., 2008; Singh et al., 2009) and due to current pricing, it is advocated as a first line insulin (NICE, 2009) but its different action profile means MATCH IT results are not necessarily comparable.

Individuals with T2DM represent a heterogeneous group with differences arising from the pathogenesis of their disease, their genotypes and phenotypes (Alsahli & Gerich, 2010). Phenotyping of patients was not possible for this study, however it is estimated that approximately 15% of individuals diagnosed as T2DM are misclassified and actually have other types of diabetes such as late-onset autoimmune diabetes or mongenic diabetes (Jones & Hattersley, 2010; Wroblewski, Gottsater, Lindgarde, Fernlund & Sundkvist, 1998) and around another 5% have mature onset diabetes of the young (MODY) indicating the individuals participating in this research may have provided a diverse group both in terms of their endogenous insulin production, and possibly their classification of diabetes. Consequently data from this group was highly dispersed for some variables and the outliers present could not be attributed to data collection errors, but more likely arose from the non-homogenous population from which sample was taken.

Moreover the inclusion of individuals with medical conditions other than T2DM was necessary to acquire a large enough sample size and does replicate the use of carbohydrate counting and flexible insulin dosing in a realistic clinical population. However results are subject to confounding from these concomitant conditions on both the primary outcomes of HbA1c and QoL questionnaire results.

5.7.2 Data analysis

Although analysis was designed to be per-protocol by only including data from participants who completed the study as per the protocol, participants adherence to flexible insulin dosing principles were not measured therefore not all participants who contributed data were using this diabetes management method consistently. This could cause underestimation of the real biological effects of carbohydrate counting and insulin dose adjustment in T2DM, but does more accurately represent individuals' imperfect and varying use of the technique. This also provides clinically useful information as individuals with T2DM are matched to insulin regimes irrespective of suitability for carbohydrate counting and flexible insulin dosing education and therefore assessing its effect as an adjunct to existing therapy is essential. An intention-to-treat analysis would be superior in clarifying the cost-effectiveness of a similar intervention in a realistic clinical situation as this would be robust against non-random participant attrition. However this study was concerned with the impact of MATCH IT on clinical and psychological parameters, rather than the practical value and cost-effectiveness of providing the intervention. In addition intention-to-treat analysis of the data would not have been possible as most participants who left the study early were either lost to follow up or declined to participate in further study procedures. This combined with the high drop-out rate for Group D rendered some data unusable, and resulted in a study that was in effect a 6 month randomised controlled trial with a control and intervention arm.

5.8 Significance of results

This exploratory study indicates that MATCH IT training is feasible for adults with T2DM and confirms the need for a large, well-designed study to fully assess its impact. This study adds to the existing literature on carbohydrate counting and flexible insulin dosing by piloting methodology in a novel patient group and providing data suitable for future power calculations on the use of this management method in individuals already treated with basal-bolus insulin. In addition it provides data regarding the psychosocial impact of this intervention in T2DM which was previously unknown. This study was not designed to definitively answer the research questions and due to the sample size and study power it is not possible to conclusively accept or reject the primary hypothesis regarding the effect on glycaemic control, but the impact of MATCH IT on one measure of QoL has been ascertained to be positive.

Extrapolating from evidence of flexible insulin dosing in T1DM and from data in this study, employing MATCH IT training in T2DM may have significant implications. This management method could improve glycaemic control and quality of life, reduce diabetes complications and result in more physiologically appropriate use of insulin, representing considerable immediate and future cost-savings to the healthcare system, as well as enhancing patients' lives. Clinical gains may be negated somewhat by increased health professional input required to teach and sustain this management technique but as in T1DM, may remain cost-effective overall (NI1CE, 2003). Intensive education is required for the success of this method, and Diabetes Specialist Dietitians play a vital role in this (Delahanty, 2010). However implementation of this education programme with suitable individuals with T2DM may overburden dietetic resources as many services already fail to meet the minimum recommended number of four full-time Diabetes Specialist Dietitians per 250,000 head of population (Diabetes UK, 2011). It is also likely that sustained user support is required; this study indicates attenuation of glycaemic control benefits may occur within 6 months possibly due to lack of continued

health professional input. Similarly insulin requirements usually alter over time and, although taught how to adjust insulin-to-carbohydrate ratios and correction factors in this and similar studies, few individuals have the confidence to do so (Lawton et al., in press) and are therefore reliant on health professionals. Interestingly however MATCH IT suggests that shorter education sessions can still be effective at educating individuals in carbohydrate counting and insulin dose adjustment.

MATCH IT data do not indicate a change clinical practice is warranted however the results suggest there no detrimental effect to clinical or psychosocial parameters arises from introducing flexible insulin dosing as a T2DM management method. This, in conjunction with its incorporation into clinical practice in some NHS services already (personal communication) despite lack of evidence of efficacy, demonstrates it can be used safely for patients struggling to integrate prandial insulin treatment with their lifestyle. Nevertheless this technique should not be used to pursue aggressive treatment goals of HbA1c <48mmol/mol whilst there is uncertainty about possible increased mortality in intensively treated older individuals with T2DM (ACCORD Study Group, 2008). The incorporation of this management method into routine clinical care for adults with T2DM on basal-bolus insulin will be dependent on future research into clinical and cost effectiveness.

As previously acknowledged weight loss would have a significant impact on glycaemic control for most individuals with T2DM however it is justifiable to explore other methods of diabetes management as it is notoriously difficult to adhere to a weight loss plan, and for those individuals predisposed to β -cell failure for whom body weight is not a major contributor to T2DM pathogenesis. MATCH IT, whilst not aiming to elicit weight loss, is very acceptable from a patient perspective as the principles do not alter whether the individual is following a weight reduction plan or not, indeed it can be used in conjunction with any eating plan or pattern. It could also appeal due to the early

improvements in QoL for users, whereas the benefit of improved glycaemic control on amelioration of risk of diabetes-related complications is neither tangible nor immediate. Furthermore intensifying glycaemic control tends to increase body weight and frequency of hypoglycaemia (ACCORD Study Group, 2008; Holman et al., 2007). Methods such as flexible insulin dosing are vital to optimise glycaemic control without deterioration of BMI or increased incidence of hypoglycaemic episodes which putatively lessen the decrement in macrovascular risk reduction arising from good blood glucose regulation (Skyler et al., 2009). Therefore despite not tackling the aetiology of T2DM, there is clearly a place for carbohydrate counting and insulin dose adjustment in some individuals with T2DM.

This flexible diabetes management method is also likely to be increasingly relevant as the incidence of T2DM increases in younger age groups (Vivian, 2006) exacerbating disease progression due to duration of diagnosis and increasing the likelihood of insulin therapy treatment. Unfortunately not all participants were able to use the carbohydrate counting and flexible insulin dosing approach in this, and similar studies (Laurenzi et al., 2011; Zipp, Roehr, Weiss & Filipetto, 2011). Since the commencement of the MATCH IT project blood glucose meters including inbuilt bolus insulin calculators and accompanying computer software for blood glucose pattern analysis have been launched. Although published evidence of their efficacy is lacking, intuitively it would appear that these devices could attenuate some of the issues of adherence to this technique such as good record-keeping and complex mental arithmetic (Lawton et al., in press). As numeracy and analytical skills would no longer be a limiting factor preventing some individuals from successfully incorporating the technique into their lives, clinical effectiveness, if achievable, is likely to be attained by the majority of motivated users of these blood glucose meters.

6. Conclusion

In conclusion MATCH IT training for adults with T2DM on a basal-bolus insulin regime enhanced quality of life and diminished perceived frequency of hypoglycaemia. This was achieved with a short group educational programme that could be realistically incorporated into routine clinical care. Carbohydrate counting and flexible insulin dosing may have improved HbA1c, even in well-controlled individuals, and is at least non-inferior to standard insulin regimes with no observed effect on most vascular risk factors despite an increase in dietary freedom. It also reduced total daily insulin doses and resulted in less weight gain compared to standard care but sustaining all positive changes over 12 months may be challenging. Use of the technique may have resulted in a small increase in the incidence of hypoglycaemia and total cholesterol but this was not clinically relevant. This feasibility study confirms the viability of training in carbohydrate counting and insulin dose adjustment for T2DM and demonstrates the technique could confer a multitude of benefits for both the individual patient and the healthcare system in the UK.

Overall the results of the MATCH IT study suggest a positive effect of carbohydrate counting and insulin dose adjustment training in adults with T2DM despite the limitations of this research. This management technique is worthy of further research to thoroughly assess its impact and a large study with an appropriate follow-up period, matched education time between groups, and possibly utilising bolus insulin calculators, is recommended.

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Appendix 1 Ethical approval



National Research Ethics Service

North West 1 Research Ethics Committee – Cheshire

Research Ethics Office
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7821

Dear Miss Fitzgerald

Study Title: Education in carbohydrate counting and flexible insulin dosing to enable increased dietary freedom in people with type 2 diabetes: a pilot randomised controlled trial of CIDAC (Carbohydrates and Insulin Dose Adjustment at the Countess)

REC reference number: 10/H1017/75

Protocol number: 8

Thank you for your letter of 8 November 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisation(s) involved in the study in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System (IRAS) or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Altered Supporting Documentation Checklist		
Response to Request for Further Information		
Letter of invitation to participant	3-Appendix 3	09 November 2010
GP/Consultant Information Sheets	2-Appendix 9 Consultant information sheet	09 November 2010
GP/Consultant Information Sheets	3 -Appendix 10 GP information sheet	09 November 2010
Protocol	8-Appendix 2	09 November 2010
Participant Information Sheet	3-Appendix 4	09 November 2010
REC application	3.0	23 September 2010
Participant Consent Form	3-Appendix 6	09 November 2010
Questionnaire: ADDQoL		
Questionnaire: DTSQs		
Questionnaire: DTSQc		
Questionnaire: W-BQ12		
Questionnaire: Researcher administered questionnaire	1 - Appendix 7	21 September 2010
Investigator CV	Dr Basma Ellahi	
Investigator CV	Dr Niru	10 September 2010

	Goenka	
Investigator CV	Miss Sarah Fitzgerald	19 September 2010
Evidence of insurance or indemnity	UMAL	01 August 2010
Referees or other scientific critique report		18 August 2010
Covering Letter		08 November 2010
Summary/Synopsis	4 - Appendix 5	19 September 2010
Letter from Sponsor	University of Chester	15 September 2010
CIDAC course content	1 - Appendix 1	21 September 2010
Co-sponsorship agreement		16 September 2010
Division of sponsorship responsibilities		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H1017/75

Please quote this number on all correspondence

Yours sincerely

PP 
Mr Jonathan Deans
Chair

Email: shehnaz.ishaq@northwest.nhs.uk

Appendix 2 Sponsorship agreement

REF: S-AHS150910



16 September 2010

Mary Fisher-Morris
Head of Research and Clinical Audit
Countess of Chester Hospital NHS Foundation Trust
Countess of Chester Health Park
Liverpool Road
Chester
Cheshire
CH2 1UL

Dear Mary

Study title: Dietary freedom and flexible insulin dosing in type 2 diabetes

Student: Sarah Fitzgerald

Chief Investigator/Academic Supervisor: Dr Basma Ellahi

I am pleased to confirm that the University of Chester has agreed to take on the role of Co-sponsor, as outlined in the Research Governance Framework for Health and Social Care, for the above research study.

The Chief Investigator is responsible for ensuring all those involved in the research project understand and fulfil their duties in accordance with the agreed protocol and any relevant management, ethical and regulatory approvals.

The University agrees to take on the following sponsorship responsibilities for the study:

- Assuring the scientific quality of proposed research;
- Ensuring the project is appropriately managed and monitored
- Promoting a quality research culture through training and the academic environment;
- Ensuring researchers understand and comply with procedures associated with their research;
- Ensuring researchers are suitably qualified to undertake the proposed research;
- Promoting maximum dissemination of research findings;
- Ensuring research ethics committee approval is obtained

All arising intellectual property will vest in and be owned absolutely by the University.

The project has been independently reviewed by the University's Faculty of Applied and Health Sciences, which has confirmed that the project is worthwhile and of scientific merit, and that the protocol describes appropriate plans for the successful completion of the research.

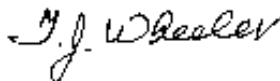
Sponsorship is conditional subject to review and approval of the research by the appropriate NHS ethics committee, R&D offices, and/or other regulatory bodies.

Please note that the University's responsibilities do not extend to assuming a duty for the care of patients. Countess of Chester Hospital NHS Foundation Trust will retain all sponsorship responsibilities relating to patient/client care and safety including associated indemnity, good clinical practice and conduct, and recording and reporting of adverse events. Schedule A provides full details of the division of Sponsor responsibilities.

I confirm that the University's public, products and employers' liability and professional indemnity insurance will apply, where appropriate, to the project. Indemnity against non-negligent harm will not be provided.

Please acknowledge receipt of this letter and confirm your acceptance of the division of responsibilities set out in Schedule A by signing and returning the enclosed copy.

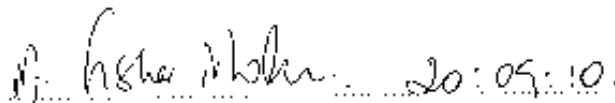
Yours faithfully



Professor T J Wheeler DL
Vice-Chancellor and Principal

CC: Research and Knowledge Transfer Office
Deputy Rursar

We acknowledge receipt of the letter of which this is a copy and agree to take on the role of Co-Sponsor with the University of Chester in accordance with the division of responsibilities set out therein



Duly authorised representative for and on behalf of
Countess of Chester Hospital NHS Foundation Trust

Please return signed copy to: Research and Knowledge Transfer Office, University of Chester
Parkgate Road, CH1 4PL

Appendix 3 Researcher-administered questionnaire

Participant Identification Number:

Data collection appointment number: 1 2 3

MATCH IT data collection tool

Date of birth:

Sex: M F

Age:

Race:

Date diabetes diagnosed.....

Medical History.....:

.....
.....
.....

Current medications and doses:.....

.....
.....
.....
.....
.....

Inclusion/exclusion criteria checked.....

Weight: kg

Waist circumference: cm

Height: m

Blood pressure: / mmHg

Diabetes Medication:.....

Long-acting insulin.....**Date started month/year**.....

Range of doses given:.....

Average dose given:.....

Short-/Quick-acting insulin..... **Date started month/year**

Range of doses: B'fast:.....Lunch:.....Dinner:.....Snacks:.....

Average dose given:.....

Average total daily insulin dose:.....

Hypoglycaemia

Episodes of mild hypoglycaemia in last month.....

Episodes of moderate hypoglycaemia in last month.....

Episodes of severe hypoglycaemia in last month.....

Lifestyle

Alcohol intake: units/week

Activity level: Sedentary Light Moderate Intense

Check Meter

HbA_{1c}.....

Total cholesterol:.....

HDL cholesterol:

Triglycerides:

Appendix 4 Participant questionnaires

ADDQoL

This questionnaire asks about your quality of life – in other words how good or bad you feel your life to be.

Please put an "X" in the box that best indicates your response for each item.

What we would like to know is how you feel about your life now.

I) In general, my present quality of life is:

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
excellent	very good	good	neither good nor bad	bad	very bad	extremely bad

Now we would like to know how your quality of life is affected by your diabetes, its management and any complications you may have.

II) If I did not have diabetes, my quality of life would be:

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
very much better	much better	a little better	the same	worse

Please respond to the more specific statements on the following pages. For each aspect of life described, you will find two parts:

For Part (a): put an "X" in one box to show how diabetes affects this aspect of your life;
For Part (b): put an "X" in one box to show how important this aspect of your life is to your quality of life.

1 (a)	If I did <u>not</u> have diabetes, I would enjoy my leisure activities:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much more	much more	a little more	the same	less
(b)	My leisure activities are:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

2	Are you currently working, looking for work or would you like to work? Yes <input type="checkbox"/> If yes, complete (a) and (b). No <input type="checkbox"/> If no, go straight to 3a.				
(a)	If I did <u>not</u> have diabetes, my working life would be:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much better	much better	a little better	the same	worse
(b)	For me, having a working life is:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

3 (a)	If I did <u>not</u> have diabetes, local or long distance journeys would be:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much easier	much easier	a little easier	the same	more difficult
(b)	For me, local or long distance journeys are:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

4	<p>Do you ever go on holiday or want to go on holiday?</p> <p>Yes <input type="checkbox"/> If yes, complete (a) and (b).</p> <p>No <input type="checkbox"/> If no, go straight to 5a.</p>
(a)	<p>If I did <u>not</u> have diabetes, my holidays would be:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very much better much better a little better the same worse</p>
(b)	<p>For me, holidays are:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very important important somewhat important not at all important</p>

5 (a)	<p>If I did <u>not</u> have diabetes, physically I could do:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very much more much more a little more the same less</p>
(b)	<p>For me, how much I can do physically is:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very important important somewhat important not at all important</p>

6	<p>Do you have any family / relatives?</p> <p>Yes <input type="checkbox"/> If yes, complete (a) and (b).</p> <p>No <input type="checkbox"/> If no, go straight to 7a.</p>
(a)	<p>If I did <u>not</u> have diabetes, my family life would be</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very much better much better a little better the same worse</p>
(b)	<p>My family life is:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very important important somewhat important not at all important</p>

7 (a)	<p>If I did <u>not</u> have diabetes, my friendships and social life would be:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very much better much better a little better the same worse</p>
(b)	<p>My friendships and social life are:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very important important somewhat important not at all important</p>

8	<p>Do you have or would you like to have a close personal relationship (e.g. husband / wife, partner)?</p> <p>Yes <input type="checkbox"/> If yes, complete (a) and (b).</p> <p>No <input type="checkbox"/> If no, go straight to 9.</p>
(a)	<p>If I did not have diabetes, my closest personal relationship would be:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very much better much better a little better the same worse</p>
(b)	<p>For me, having a close personal relationship is:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very important important somewhat important not at all important</p>

9	<p>Do you have or would you like to have a sex life?</p> <p>Yes <input type="checkbox"/> If yes, complete (a) and (b).</p> <p>No <input type="checkbox"/> If no, go straight to 10a.</p>
(a)	<p>If I did not have diabetes, my sex life would be:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very much better much better a little better the same worse</p>
(b)	<p>For me, having a sex life is:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very important important somewhat important not at all important</p>

10 (a)	<p>If I did not have diabetes, my physical appearance would be:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very much better much better a little better the same worse</p>
(b)	<p>My physical appearance is:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very important important somewhat important not at all important</p>

11 (a)	<p>If I did not have diabetes, my self-confidence would be:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very much better much better a little better the same worse</p>
(b)	<p>My self-confidence is:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>very important important somewhat important not at all important</p>

12 (a)	If I did <u>not</u> have diabetes, my motivation would be:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much better	much better	a little better	the same	worse
(b)	My motivation is:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

13 (a)	If I did <u>not</u> have diabetes, the way people in general react to me would be:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much better	much better	a little better	the same	worse
(b)	The way people in general react to me is:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

14 (a)	If I did <u>not</u> have diabetes, my feelings about the future (e.g. worries, hopes) would be:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much better	much better	a little better	the same	worse
(b)	My feelings about the future are:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

15 (a)	If I did <u>not</u> have diabetes, my financial situation would be:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much better	much better	a little better	the same	worse
(b)	My financial situation is:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

16 (a)	If I did <u>not</u> have diabetes, my living conditions would be:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much better	much better	a little better	the same	worse
(b)	My living conditions are:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

17 (a)	If I did <u>not</u> have diabetes, I would have to depend on others when I do not want to:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much less	much less	a little less	the same	more
(b)	For me, not having to depend on others is:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

18 (a)	If I did <u>not</u> have diabetes, my freedom to eat as I wish would be:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much greater	much greater	a little greater	the same	less
(b)	My freedom to eat as I wish is:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

19 (a)	If I did <u>not</u> have diabetes, my freedom to drink as I wish (e.g. fruit juice, alcohol, sweetened hot and cold drinks) would be:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	very much greater	much greater	a little greater	the same	less
(b)	My freedom to drink as I wish is:				
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	very important	important	somewhat important	not at all important	

If there are any other ways in which diabetes, its management and any complications affect your quality of life, please say what they are below:

Thank you for completing this questionnaire.

Diabetes Treatment Satisfaction Questionnaire (change): DTSQc

Six months ago you received training in insulin adjustment and carbohydrate counting. Today we would like to know how your experience of your current treatment (including insulin adjustment and carbohydrate counting) has changed from your experience of treatment before the training began 6 months ago. Please answer each question by circling a number on each of the scales to indicate the extent to which you have experienced changes. If you have experienced no change, please circle '0'.

1. How satisfied are you with your current treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now
----------------------------	---	---	---	---	----	----	----	----------------------------

2. How often have you felt that your blood sugars have been unacceptably high recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now
------------------------------	---	---	---	---	----	----	----	------------------------------

3. How often have you felt that your blood sugars have been unacceptably low recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now
------------------------------	---	---	---	---	----	----	----	------------------------------

4. How convenient have you been finding your treatment to be recently?

much more convenient now	3	2	1	0	-1	-2	-3	much less convenient now
-----------------------------	---	---	---	---	----	----	----	-----------------------------

5. How flexible have you been finding your treatment to be recently?

much more flexible now	3	2	1	0	-1	-2	-3	much less flexible now
---------------------------	---	---	---	---	----	----	----	---------------------------

6. How satisfied are you with your understanding of your diabetes?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now
----------------------------	---	---	---	---	----	----	----	----------------------------

7. How likely would you be to recommend your present treatment to someone else with your kind of diabetes?

much more likely to recommend the treatment now	3	2	1	0	-1	-2	-3	much less likely to recommend the treatment now
---	---	---	---	---	----	----	----	---

8. How satisfied would you be to continue with your present form of treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now
----------------------------	---	---	---	---	----	----	----	----------------------------

Please make sure that you have circled one number on each of the scales.

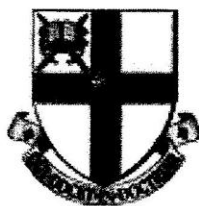
Well-Being Questionnaire (W-BQ12)

Please circle one number on each scale, from 3 (all the time) to 0 (not at all), to indicate how often you feel each statement has applied to you in the past few weeks.

	all the time	not at all
1. I have crying spells or feel like it	3	2 1 0
2. I feel downhearted and blue	3	2 1 0
3. I feel afraid for no reason at all	3	2 1 0
4. I get upset easily or feel panicky	3	2 1 0
5. I feel energetic, active or vigorous	3	2 1 0
6. I feel dull or sluggish	3	2 1 0
7. I feel tired, worn out, used up or exhausted	3	2 1 0
8. I have been waking up feeling fresh and rested.....	3	2 1 0
9. I have been happy, satisfied or pleased with my personal life.....	3	2 1 0
10. I have lived the kind of life I wanted to.....	3	2 1 0
11. I have felt eager to tackle my daily tasks or make new decisions	3	2 1 0
12. I have felt I could easily handle or cope with any serious problem or major change in my life.....	3	2 1 0

Please make sure that you have considered each of the 12 statements and have circled one number in response to each statement.

Appendix 5 Participant questionnaire agreement



University of
Chester

To: Clare Bradley PhD,
Professor of Health Psychology,
Dept of Psychology,
Royal Holloway,
University of London,
Egham, Surrey, TW20 0EX.

Re: Application for a Licence to use: ADDQoL-19
DTSQs
DTSQc
W-BQ12

Study Title: Education in carbohydrate counting and flexible insulin dosing to enable increased dietary freedom in people with type 2 diabetes: a pilot randomised controlled trial of CIDAC (Carbohydrates and Insulin Dose Adjustment at the Countess).

Student Name and Title: Miss Sarah Fitzgerald

Student Status: Part-time postgraduate

Supervisor's Name and Title: Dr Basma Ellahi

Supervisor's Position: Head of the Department of Clinical Sciences

Department: Department of Clinical Sciences

I declare that I am supervising **Sarah Fitzgerald**, who is a registered student at the university, in the above study and that the study is not commercially funded*.

Signed:

Basma Ellahi

Date:

27.9.2010

Signed (by student):

SB

Date:

27/9/10

* "Commercially funded" means a monetary contribution from a commercial organisation. Grants and contributions from Foundations, Charities and Academic Institutions are excluded.

14th September 2010

(1) HEALTH PSYCHOLOGY RESEARCH LTD

(2) DR BASMA ELLAHI

And (3) MISS SARAH FITZGERALD

Ref: CB76

AGREEMENT

for the use of the **Audit of Diabetes Dependent Quality of Life (ADDQoL19)** (Standard UK English (rev. 1.3.06)), **Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs)** (Standard UK English (rev. 7/94)), **Diabetes Treatment Satisfaction Questionnaire (change) (DTSQc)** (Standard UK English (rev. 4.3.98; generic intro. rev. 28.2.02. Instructions adapted 14.9.10 for study ref. CB76)) and **Well-Being Questionnaire (W-BQ12)** (Standard UK English (instructions rev. 31.1.02)) in a study of 'Training in flexible, intensive insulin management to enable increased dietary freedom in people with type 2 diabetes: A pilot randomised controlled trial of CIDAC (Carbohydrates and Insulin Dose Adjustment at the Countess)' at Countess of Chester Hospital NHS Trust, Chester and University of Chester

Please return TWO signed copies of this Agreement to:
Mrs Janet Bayfield
Health Psychology Research Ltd
Department of Psychology
Royal Holloway, University of London
Egham, Surrey, TW20 0EX, U.K.

THIS AGREEMENT dated 14th September 2010 is made **BETWEEN:**

- (1) **HEALTH PSYCHOLOGY RESEARCH LTD.**, Orchard Building, Royal Holloway, University of London, Egham, Surrey TW20 0EX ("HPR Ltd"); and
- (2) **DR BASMA ELLAHI** of Department of Clinical Sciences, University of Chester, Parkgate Road, Chester CH1 4BJ (Dr Basma Ellahi) ("Licensee")
- (3) **MISS SARAH FITZGERALD** of University of Chester, Parkgate Road, Chester CH1 4BJ (Miss Fitzgerald) ("Licensee").

Together, parties (2) and (3) "Licensees"

WHEREAS:

- Licensees intend to carry out a study using questionnaire(s) in which the copyright is owned by Prof Clare Bradley (Prof Bradley), and
- Prof Bradley has authorised HPR Ltd to sub-licence her questionnaires, and
- HPR Ltd agrees to grant Licensees a licence to use questionnaire(s) defined below, strictly on a non-commercial basis in the study described in the Protocol attached hereto subject to the terms of this agreement.

NOW THEREFORE THE PARTIES HEREBY AGREE AS FOLLOWS:

1. Definitions

1.1 "Questionnaire(s)" shall mean:

- **Audit of Diabetes Dependent Quality of Life (ADDQoL19)** (Standard UK English (rev. 1.3.06))
- **Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs)** (Standard UK English (rev. 7/94))
- **Diabetes Treatment Satisfaction Questionnaire (change) (DTSQc)** (Standard UK English (rev. 4.3.98; generic intro. rev. 28.2.02))
- **Well-Being Questionnaire (W-BQ12)** (Standard UK English (instructions rev. 31.1.02))

and any modifications thereto or any adaptations or translations thereof.

1.2 "Study" shall mean 'Training in flexible, intensive insulin management to enable increased dietary freedom in people with type 2 diabetes: A pilot randomised controlled trial of CIDAC (Carbohydrates and Insulin Dose Adjustment at the Countess)' as set out in the Protocol attached hereto.

1.3 "Licence Period" shall mean from the date of the last signature to this Agreement until one year after the completion of the Study, or until three years from the date of last signature, whichever shall be sooner.

2. Copyright and Licences Thereto

2.1 Ownership of all copyrights in the Questionnaire(s) vests in Prof Bradley, and nothing in this Agreement shall be construed either expressed or implied as conferring any transfer of or rights of ownership upon Licensees in the Questionnaire(s).

2.2 Prof Bradley hereby grants to Licensees a non-exclusive non-transferable royalty-free licence during the Study to use the Questionnaire(s) only for their own internal non-commercial research purposes to:

- use the Questionnaire(s) in the Study;
- make copies of the Questionnaire(s) from a master copy submitted to them only where reasonably necessary for the purpose of carrying out the Study. The integrity of the Questionnaire(s) is important and Licensees undertake to make no alterations or amendments of any kind to the Questionnaire(s) (including but not limited to, shrinking by photocopier or scanner), and that they will be used in the Study exactly as supplied unless expressly agreed in writing in advance with Prof Bradley. Amendment is any alteration to the wording, format or font as supplied, or any transfer of the Questionnaire(s) to a different medium, including but not limited to an electronic format or web page. If the Questionnaire(s) are amended in any way, once such amendment is expressly agreed in writing, Licensees will supply Prof Bradley with an amended version of the Questionnaire(s) for approval. Licensees hereby agree not to use an amended version of the Questionnaire(s) until Prof Bradley has expressly approved the amended version in writing. Questionnaire(s) for amendment will be supplied by HPR Ltd in pdf format.

Licensees undertake not to supply nor to make available to any third party any Questionnaire(s), instructions or translations thereof supplied under this Agreement, including but not limited to, the publication in or attachment to any website or e-mail, except that for the purposes of the Study. Questionnaire(s) may be inserted into a website accessible only to parties to this Agreement and participants in the Study;

- supply to respondents only the number of copies of the Questionnaire(s) as is strictly necessary for the purpose of carrying out the Study. If you have to distribute additional Questionnaire(s) to other administrators the additional Questionnaires should have a covering letter with the following statement (this statement should be in the covering letter to administrators of the questionnaire not to patients and not included in the Questionnaires themselves):

"Copyright in these questionnaires is owned by Prof Clare Bradley of Health Psychology Research Ltd. Your use of the questionnaires is strictly limited to the particular study you are undertaking for Dr Basma Ellahi and Miss Fitzgerald and you are not authorised to make additional copies of the questionnaires without the express written permission of Prof Bradley. These questionnaires are in continual development and it is important to ensure that any new study uses the most up-to-date version. Please contact Prof Bradley if you require further information about the questionnaires and their continued development or if you wish to make further use of the questionnaires outside the scope of the study you are undertaking for Dr Basma Ellahi and Miss Fitzgerald."

2.3 Questionnaire(s) may be provided "For Information". These are intended for review and assessment, and may be used for submission to Ethics Committees and Review Boards. "For Information" Questionnaire(s) should be used for inclusion in protocols, manuscripts and theses and attention should be drawn to the copyright statement on the questionnaire(s) directing future potential users to www.healthpsychologyresearch.com for access to the questionnaire(s).

- 2.4 **"For Use" Questionnaire(s) may be used only in the study for which they are licensed. They may not be sent to Ethics Committees or Review Boards, included in protocols, manuscripts or theses (where "For Information" Questionnaires are the only versions that can be included) or passed on to others, except for the purposes of the study for which they have been licensed.**

3. Acknowledgements

- 3.1 Licensees hereby undertake to acknowledge the source of the Questionnaire(s) in any communication reporting on their use or any publication generated directly or indirectly through use of the Questionnaire(s).

4. Publication

- 4.1 Licensees shall in confidence supply Prof Bradley with a copy of the text of any proposed communication or publication concerning the Questionnaire(s) authored by Licensees or research collaborators to whom they send copies of the Questionnaire(s), no later than thirty days prior to any proposed submission for publication or dissemination of the same.

5. Representations, Liability and Indemnities

- 5.1 Licensees understand that the Questionnaire(s) are experimental in nature. Neither Prof Bradley nor HPR Ltd make any representations or extend any warranties of any kind, either express or implied, as to the quality or fitness for a particular purpose of the Questionnaire(s) or concerning any advice or information relating to the Questionnaire(s) and their use.
- 5.2 Neither Prof Bradley nor HPR Ltd shall be liable in any way for the use made of the Questionnaire(s) by Licensees pursuant to licences granted to it under this agreement, and Licensees hereby agree to defend, indemnify, and hold Prof Bradley and HPR Ltd harmless from any loss, claim, damage, or liability howsoever caused arising out of any of Licensees research projects involving the Questionnaire(s).

6. Termination

- 6.1 This Agreement may be terminated by HPR Ltd with immediate effect by giving written notice to the Licensees if:
- 6.1.1 either Licensee is in breach of any provision of this Agreement and (if it is capable of remedy) the breach has not been remedied within 30 days after the Licensees have received a notice specifying the breach and requiring its remedy; or
- 6.1.2 there is any unreasonable delay in starting or completing the Study.
- 6.2 On termination of this Agreement the Licence Period will automatically come to an end and any licences granted under this Agreement shall terminate.

Health Psychology Research Ltd


.....
Prof Bradley

Director of HPR Ltd

Position

15th Sept. 2010
.....
Date

Dr Basma Ellahi


.....
Dr Basma Ellahi

Head of Dept of Clinical Sciences

Position

28.10.10
.....
Date

Miss Sarah Fitzgerald


.....
Miss Fitzgerald

MSc Student

Position

18th October 2010
.....
Date

PROTOCOL

(Important – the Protocol sets out the scope of the study and must be appended hereto)

\\StudentStudyAgmt\\Rev.26.1.09

Appendix 6 Participant invitation letter



Diabetes Unit
Countess of Chester Hospital NHS
Foundation Trust
Countess of Chester Hospital
Health Park,
Liverpool Road
Chester CH1 2UL

Date 26th November 2010

««AddressBlock»»

««GreetingLine»»

Research looking at dietary freedom and flexible insulin dosing in type 2 diabetes: MATCH IT (MAtching Treatment to CarboHydrates in Insulin-treated Type 2 diabetes)

The University of Chester and the Countess of Chester Hospital are working together to do a research study and are writing to you to ask if you would be willing to take part. The project is looking at the way people with diabetes manage their condition and is investigating a new way of controlling blood glucose levels by matching the insulin doses you give yourself to the food that you eat. This can also allow more dietary freedom. We hope this will help us see if more flexible treatments are possible for people with type 2 diabetes.

Why have I been asked?

You have been chosen because you have type 2 diabetes and take a certain type of insulin. You are one of a large number of people from the hospital that we are asking to help.

What would I have to do?

If you agree to take part, it would involve making at least three visits in one month to the Countess of Chester Hospital where you would receive training in a group and on a one-to-one basis. We aim to teach you how to match the insulin you inject to the food you eat. You would also make three other visits over the course of a year to allow us to collect some information about you. The researchers would ask you some questions about your diabetes, give you a questionnaire to fill in and you would have your blood pressure, height and weight measured, and we would take a blood sample. The researchers will reimburse you for travel expenses for all your visits.

How do I reply?

If you think you might want to know more, you can register your interest in one of these ways:

1. You could complete the reply-slip and return it to us. A researcher will contact you to discuss the study.
2. You can telephone 01244 366 581 and leave a message on the answer machine of the study dietitian, Sarah Fitzgerald, and she will return your call. Please note messages are not always picked up daily.

If you are interested in taking part the researchers will give you more details about the study. By contacting us you will not be under any obligation to take part, and you will be free to change your mind at any time.

If you are not interested in taking part in the study, we would be grateful if you could complete the reply-slip and we will not contact you.

If you have any questions please contact Sarah Fitzgerald, the study dietitian, on 01244 366 581. The researchers look forward to hearing from you.

Yours sincerely,

Sarah Fitzgerald
Dietitian

I am interested in knowing more about the MATCH IT study looking at dietary freedom and flexible insulin dosing in type 2 diabetes

☐

I am **NOT** interested in knowing more about the MATCH IT study looking at dietary freedom and flexible insulin dosing in type 2 diabetes

☐

My name is.....

The first line of my address is.....

Please contact me on this telephone number.....

Or this telephone number.....

Between the times of.....

Appendix 7 Participant information sheet



Information about the Research

A feasibility study of carbohydrate counting and flexible insulin dosing in adults with type 2 diabetes:

MATCH IT (MAtching Treatment to CarboHydrate in Insulin-treated type Two diabetes)

We would like to invite you to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. **One of our team will go through the information sheet with you and answer any questions you have.** We'd suggest this should take about 10 minutes.

This copy of the information sheet is yours to keep. Should you decide to take part, a copy of the consent form you have signed will also be yours to keep.

Talk to others about the study if you wish. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Ask us if there is anything that is not clear.

Part 1. The study purpose

We want to investigate a new way of controlling your blood glucose levels by matching the insulin doses you give yourself to the food that you eat. This has not been tested extensively in people with type 2 diabetes but is an option in standard care for people with type 1 diabetes.

By the end of this research it is hoped that you will be able to recognise the foods that affect your blood glucose levels, the carbohydrates, and to calculate the quantity of them that you plan to eat at each meal. You will then be able to calculate your exact insulin dose required for that meal.

Doing this should give you freedom to eat the quantities of carbohydrate that you want, without having to choose standardised portions to match your prescribed insulin. Your insulin doses will be tailored to your diet and lifestyle rather than your diet and lifestyle fitting around your insulin doses.

We plan to teach you to be able to do this in two interactive and informal group education sessions, each of 3 hours duration, on two consecutive weeks followed by one 30 minute appointment one-to-one with a dietitian.

Why have I been invited?

You have been invited because your health records identified you as a person who has had type 2 diabetes and who injects a rapid-acting or short-acting insulin (Novorapid, Humalog, Actrapid or Humulin S).

Do I have to take part?

It is up to you to decide if you join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time throughout the study, without giving a reason. This would not have any consequences for you, nor would affect the standard of care you receive and you can return to your usual insulin prescription.

What will happen to me if I take part?

This study is a pilot of a randomised trial which means we are testing a way of investigating something. Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each participant is put into a group by chance (randomly).

In our study, we want to compare your usual insulin prescription to a more flexible one, determined by what you eat. Everyone invited to take part in the study will have the chance to be taught how to change their own insulin doses. Some people will be taught this at the start of the study and some people six months later. This allows us to compare the people who have received the education, who are changing their own insulin doses, with the people who are still waiting to attend the education and using their usual insulin prescriptions.

If you decide to take part, you will be randomised to either attend the education sessions immediately, or to attend them in 6 months time. You have a 50% chance of being invited to start the education immediately. No matter which group you are put into, we would like to collect information about you at the start of our study and after 6 and 12 months.

To collect information, we will invite you to attend an appointment at the Countess of Chester Hospital. Your appointment will last approximately an hour and you will see a researcher (likely a dietitian), a clinic nurse and a phlebotomist, whose job it is to take blood samples.

The information we would like to collect will come from a blood sample, a questionnaire you fill in, questions we will ask you and your height, weight, waist circumference and blood pressure.

You will be involved in the study for 12 months in total. After you have attended the education sessions, you will hopefully know how to change your insulin doses to match the food you eat and you will go back to usual monitoring by diabetes healthcare professionals. If at any time, you would like to see a healthcare professional about what you have been taught as part of this research, you can contact us.

Expenses

As a thank you for taking time to take part in our study, we will offer you the chance to claim back the cost of travelling to the hospital and parking, if applicable, up to £5 each way.

What will I have to do?

If you decide to take part in the study, please be sure you can commit to attending the three appointments, during which we will gather information about you, and the two group education sessions, each of three hours duration, plus a one hour appointment with the dietitian. This makes six visits to the Countess of Chester Hospital in total.

After the first education session we will ask you to monitor your blood glucose levels at home more often than you may do now, and to write this down, together with the amount of carbohydrate that you eat, and the insulin dose that you give yourself. We will give you a diary to enable you to do this. This helps us personalise the information we give you at the second group education session.

Throughout this study, we ask that you continue to take your usual medication at your usual times. We will only teach you to change the amount of insulin that you give yourself, all other doses of your medications should remain as your doctor has prescribed them.

What are the possible disadvantages and risks of taking part?

The disadvantage of taking part is the amount of time we will take to gather information from you and to teach you how to match your insulin doses to your food. It may be an inconvenience to you to attend these appointments and education sessions.

The blood sample we will take will be no different than a normal blood sample requested by your doctor so this should be no more uncomfortable than usual. We will ask that you monitor your blood glucose levels more often at home and doing this can sometimes cause sore fingers.

There is a risk that you may have more episodes of hypoglycaemia (low blood glucose levels) than usual. As part of the education we will discuss how to avoid, identify and treat hypoglycaemia. There is also a risk that you may gain weight. This is because we are showing you how to increase your dietary freedom whilst keeping your blood glucose levels close to the normal range so you will be able to eat whatever you choose. This could include high-fat, high-sugar foods you may have previously avoided. If you eat more calories than you need in a day, you will gain weight, just as someone without diabetes would. The education is not about healthy eating but we would still encourage a balanced diet. On the other hand, it is possible to use this education to reduce the amount you eat, without a greater risk of hypoglycaemia, and this can help with weight loss.

What are the side effects of any treatment received when taking part?

There will be no side effects due only to taking part in this research. The side effects of taking insulin will remain the same and these should be discussed with your doctor if required.

Harm to the unborn child

There should be no harm to an unborn child as a result of changing insulin doses to match the food you eat, however pregnant women are not eligible to take part in this study. If you were to become pregnant, you should inform the study researcher and your doctor immediately.

What are the possible benefits of taking part?

We cannot promise this study will help you but the information we get from this study may help improve the treatment of people with type 2 diabetes.

This study may give you a greater understanding of your diabetes and how the food you eat, in particular the carbohydrates, affects your blood glucose levels. It may give you the knowledge and confidence to change your insulin doses based on what you are eating, which can change day-to-day and meal-to-meal, rather than injecting your prescribed insulin dose.

Doing this should give you freedom to eat the quantities of carbohydrate that you want, without having to choose portions to match your prescribed insulin. Your insulin doses will be tailored to your diet and lifestyle, rather than your diet and lifestyle fitting around your insulin doses.

This does not mean that we no longer recommend eating a healthy balanced diet but this method allows you to have more flexibility in your diet while still being able to keep your blood glucose levels well controlled. In fact, after this study, you may find your blood glucose levels improve because you are giving yourself more personalised insulin doses and this could reduce the risk of you developing diabetes-related health problems such as damage to your heart, kidneys and eyes.

This completes Part 1. If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2.

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study he/she may ask you to sign an agreement outlining the discussion.

What will happen if I don't want to carry on with the study?

You are free to withdraw at any time throughout the study, without giving a reason. This would not have any consequences for you nor would it affect the standard of care you receive and you can return to your usual insulin prescription if you wish.

You can withdraw from the study but still keep in contact with us to let us know your progress. Information collected may still be used unless you tell us not to. If you wish to completely withdraw from the study, we may continue to use the data we have already collected from you, unless you tell us not

to. At any point in the study, and up until we analyse our data, you have the right to ask us to destroy the data that we hold on you and not include it in our study results.

What if I have a complaint?

If you have a concern about any aspect of this study, you should ask to speak to the researcher who will do her best to answer your questions. Please contact Sarah Fitzgerald, Dietitian on 01244 366 581. If you remain unhappy, or do not want to speak to a researcher, and wish to complain formally about this study, you can do this through the University of Chester complaints procedure by writing to the Dean of Applied and Health Sciences, Professor Sarah Andrew. Further details can be obtained from the University of Chester on 01244 511000.

Alternatively, if you wish to make a complaint regarding the standard of healthcare you have received, please contact PALS, the Countess of Chester Hospital Patient Advice and Liaison Service. You can phone the PALS manager on 01244 366066. To make a formal complaint, you can also write to the Chief Executive of the Trust, Peter Herring.

What if something goes wrong?

In the unlikely event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Chester or the Countess of Chester Hospital NHS Foundation Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised. You can ask to see the data we hold on you, to check it for errors.

Your data will be stored on a computer database, but your details will be coded so that it will not be possible to identify you from the data we hold on the database. We will have a paper hard copy of your personal details, together with your code, which will identify data as yours should we need to do this. This will be secured in a locked drawer, in a locked room at all times not in use, and only authorised researchers will have access to your identifiable data. A password-protected electronic copy of this will be stored on an NHS computer network with a password protected log-in so it will not be possible for others to find out your identity from your coded data.

Your coded data will be kept securely for 10 years then destroyed confidentially. The data you provide may be used in the future, but it will not be possible for others to find out your identity from your coded data in the future. You need to inform us if you do not wish your anonymous data to be used in future research.

Involvement of the General Practitioner (GP)

A diabetes consultant at the Countess of Chester Hospital will have assessed you for eligibility before we invited you to take part in this research. He will also be notified that you have agreed to take part if you decide to. Once you have completed the education sessions as part of this research, we will write to your GP to let them know that you have attended this course and that you may now wish to change your own insulin doses.

What will happen to any samples I give?

You will be asked to give blood samples specifically for the purpose of monitoring the effect of this study. These blood samples will be destroyed in line with Countess of Chester Hospital policy and will not be retained for the purpose of this study. The results of your blood tests will be available on our hospital database so any healthcare professional involved in your care can view them.

What will happen to the results of the research study?

Your individual results indicating your blood glucose control and cholesterol levels from blood samples collected at the start of the study, at 6 months and at 12 months will be shared with you by letter.

The broader findings from our research will hopefully be published in a scientific journal and/or presented at a conference. You will not be identified in any publication or presentation. A summary of our research findings will be shared by letter with all the people who took part in the research.

Who is organising and funding the research?

The research is being carried out in part by Sarah Fitzgerald, Dietitian, as part of a study for a Masters degree in Nutrition and Dietetics.

The University of Chester and the Countess of Chester Hospital NHS Foundation Trust are sponsoring the research. Funding applications are in progress but no funding has yet been secured.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by North West England Strategic Health Authority Research Ethics Committee.

Further information and contact details

For general information on research, see the Diabetes UK website, the Medical Research Council website or the NHS Choices websites.

www.diabetes.org.uk/Research

www.nhs.uk/conditions/clinical-trials

www.ctu.mrc.ac.uk/TakePart

For specific information on this study, or advice regarding whether to participate, contact Sarah Fitzgerald, Dietitian on 01244 366 581. Your GP can also advise you about participating in this study.

Appendix 8 Participant consent form



Participant Identification Number:

CONSENT FORM

A feasibility study of carbohydrate counting and flexible insulin dosing in adults
with type 2 diabetes:

**MATCH IT (MATCHing Treatment to CarboHydrate in Insulin-treated type Two
diabetes)**

Name of Researcher: Sarah Fitzgerald

Please initial box

1. I confirm that I have read and understand the information sheet dated 2.2.11 version 4 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Chester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

☐

4. I agree to my GP being informed of my participation in the study.

☐

5. I agree to take part in the above study.

☐

Name of Participant:

Date:

Signature:

Name of Person taking consent:

Date:

Signature:

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Appendix 9 Carbohydrate counting and insulin dose adjustment calculations

Calculating insulin-to-carbohydrate ratios and correction factors

Estimates of personalised insulin-to-carbohydrate ratios and correction factors were calculated from participants' blood glucose and food diaries then further adjusted as required based on blood glucose monitoring feedback. Insulin-to-carbohydrate ratios and correction factors may vary at different times of the day.

Insulin-to-carbohydrate portion (insulin:CP) ratio =

$$\frac{\text{Carbohydrate consumed (carbohydrate portions or CPs)}}{\text{Insulin dose (units)}}$$

Correction factor =

$$\frac{100}{\text{Total daily dose of insulin (units)}}$$

Calculating meal-time insulin doses

Meal-time insulin dose =

Insulin:CP ratio x CPs +

(Δ blood glucose level to achieve pre-meal target x correction factor) +

% increase or decrease for physical activity/stress/illness

Appendix 10 GP information letter



A feasibility study of carbohydrate counting and flexible insulin in people with type 2 diabetes: MATCH IT (MAatching Treatment to CarboHydrate in Insulin-treated type Two diabetes)

Diabetes Centre (OPD 3)
Countess of Chester Hospital NHS
Foundation Trust,
Countess of Chester Hospital Health
Park,
Liverpool Road,
Chester,
CH1 2UL

Date

Dear Dr (GP name),

Patient name:

Date of birth:

Address:

Hospital number:

Your patient has agreed to take part in a feasibility study. The research is investigating the effect of an educational intervention promoting flexibility of insulin doses and dietary freedom in people with type 2 diabetes on rapid- or short-acting insulin. The project will trial methodology designed to assess the impact of carbohydrate counting and insulin dose adjustment on quality of life, satisfaction with treatment and glycaemic control. This project involves a delayed start method and aims to compare standard care (the delayed start group prior to the intervention) to the effect of the educational intervention. This patient has been allocated to the:

Immediate start group commencing education shortly

☐

Delayed start group commencing education 6 months after baseline

☐

As part of the study the patient will be taught to adjust their own insulin doses in relation to dietary carbohydrate intake. The patient will be attending the Countess of Chester Hospital for one follow-up appointment after the education and will then return to standard care. The patient can contact the researchers at any time for additional support if required.

We would be very grateful if you would continue to prescribe and monitor all their medication, including their insulin, as before. Please do not hesitate to contact the study dietitian, Sarah Fitzgerald, on 01244 366 581 if you have any queries.

Yours sincerely,

Sarah Fitzgerald
Dietitian

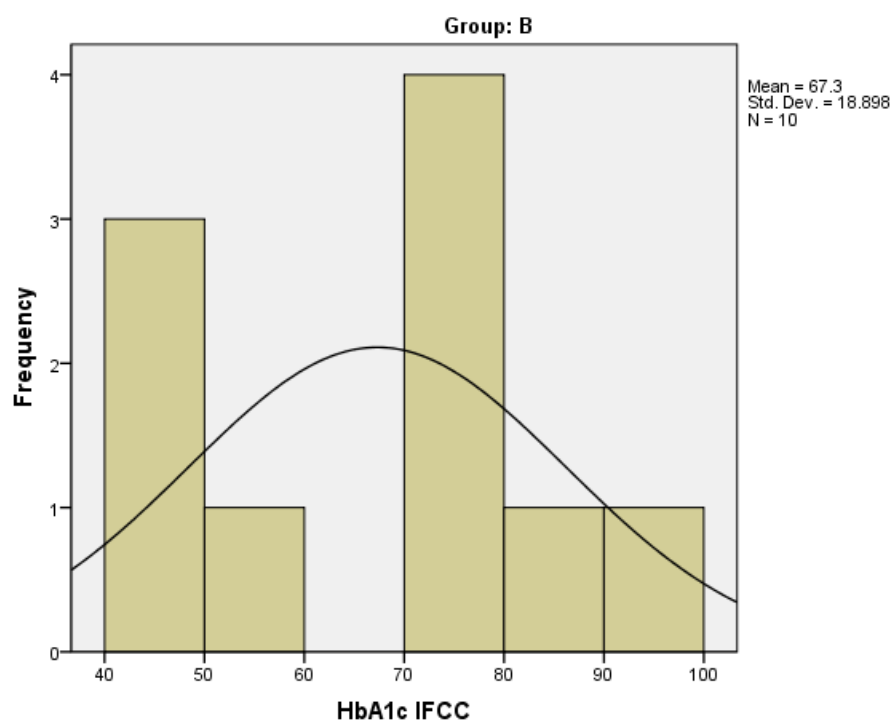
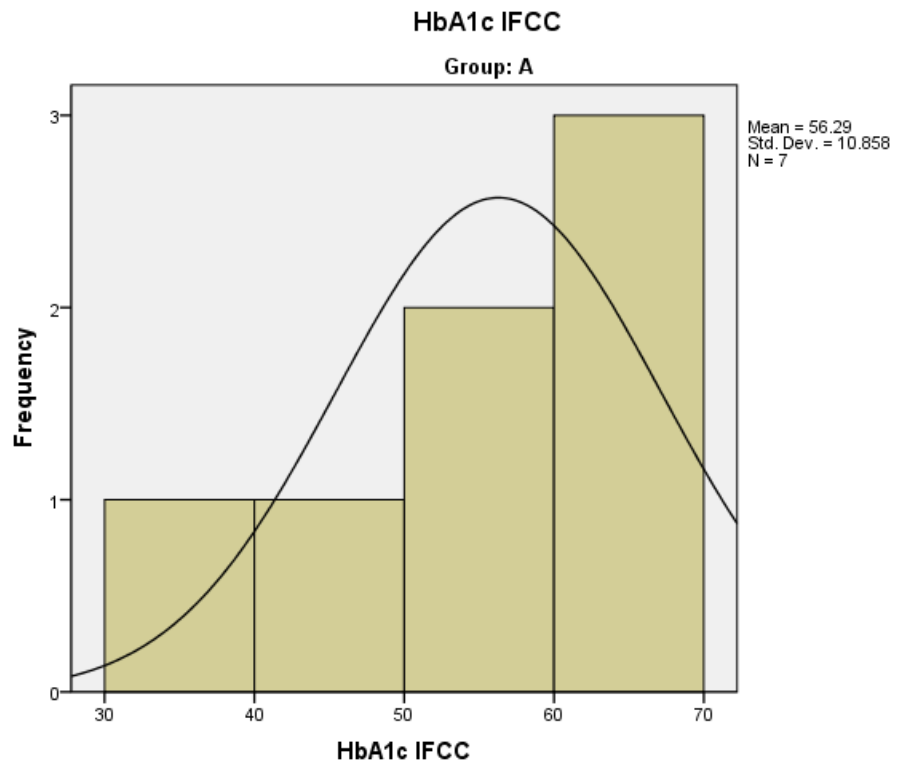
Appendix 11 Normality tests and graphs

Tests of Normality

Group		Kolmogorov-Smirnov ^a			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
A	HbA1c IFCC	.204	7	.200*	.938	7	.622
B	HbA1c IFCC	.214	10	.200*	.902	10	.231

a. Lilliefors Significance Correction

*. This is a lower bound of the true significance.



Normal Q-Q Plot of HbA1c IFCC

